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ZUR ELEKTRODENANORDNUNG BEI DEN REGISTRIERUNGEN BIOELEKTRISCHER POTENTIALSCHWANKUNGEN DER HIRNRINDE*

A. E. KORNMÜLLER UND J. A. SCHAEDER
Aus dem Kaiser-Wilhelm-Institut für Hirnforschung, Berlin-Buch.

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I. Einleitung

Nachdem in den letzten Jahren ein grösseres Material über die lokalisierten bioelektrischen Erscheinungen der Hirnrinde† gesammelt worden ist, ist es an der Zeit, eine weitere Analyse des Kurvenbildes anzustreben. Damit soll in der vorliegenden Mitteilung begonnen werden.

Folgende Arten von Ableitungen finden beim Studium der bioelektrischen Erscheinungen des Gehirns Verwendung:

1. Die enge bipolare Ableitung. Diese besteht darin, dass man beide Elektroden knapp nebeneinander auf die Hirnrinde legt oder dass man mittels einer konzentrischen Elektrode ableitet.

2. Die unipolare Ableitung. Bei dieser wird die differente Elektrode auf die abzuleitende Hirnrindenstelle und die indifferente auf eine Stelle des Schädels, welche selbst keine bioelektrischen Erscheinungen aufweist, gelegt. Dafür kommt der Schädelknochen in Frage, z. B. das blossliegende Stirn- und Nasenbein und die Protuberantia occipitalis externa.

Diese beiden Ableitungsarten sind für lokalisatorische Fragen geeignet. Die Beziehungen zwischen den Kurvenbildern, die diese beiden Ableitearten ergeben, sollen hier in erster Linie untersucht werden.

3. Die Ableitung nach Berger, bei welcher bekanntlich die beiden Elektroden entweder auf Stirn und Hinterhaupt oder aber bitemporal gelegt werden. Diese Ableitung erfolgt in der Regel von der Oberfläche der Kopfschwarte.

Nach viel verbreiteten Auffassungen sind für die beiden erstgenannten Ableitungsarten folgende Vorteile und Nachteile zu erwarten:

Die enge bipolare Ableitung hat vor allem den Vorteil, dass sie die grösste Gewähr dafür gibt, dass nur die Potentialschwankungen der zwischen den Elektroden liegenden Hirnpartien registriert werden. Aus morphologischen wie physikalischen Gründen wäre anzunehmen, dass eng benachbarte Stellen mehr oder weniger gleichzeitig erregt werden können, so dass zwischen diesen Stellen kein grosses Potentialgefälle erwartet werden kann. Bei zu engem Elektrodenabstand werden ja auch die Amplituden der elektrischen Potentialschwankungen sehr klein, so dass sie sich von dem Störspiegel des Apparates eventuell nicht genügend abheben. Die Schwankungen grosser Amplitude, die das Summationsprodukt der Spannungspro-

* Mit Unterstützung der Rockefeller-Foundation.
† Siehe A. E. Kornmüller, 1937(a)!

duktion vieler Elemente darstellen, sind über bestimmten Feldern, z.B. der Area striata, innerhalb grösserer Strecken mehr oder weniger synchron in ihrem Verlauf, wie die unipolare Ableitung ergibt. Sie werden darum bei enger bipolarer Ableitung mit kleinsten Elektrodenabständen kaum registriert. Dafür beherrschen kleine rasche Schwankungen das Bild. Dabei könnte es sich um die erwähnten Einzelentladungen handeln. Grössere Elektrodenabstände bei der bipolaren Ableitung bringen wiederum die Gefahr mit sich, dass die Elektroden gleichzeitig von strukturell (architektonisch) differenten Gebieten ableiten. Dies gilt besonders dann, wenn im Bereiche kleiner architektonischer Felder, wie sie z.B. am Kaninchen zahlreich sind, oder in der Nähe architektonischer Grenzen abgeleitet wird. Die Lage der Elektroden in bezug zur architektonischen Gliederung der Hirnrinde muss aber unter allen Umständen festgestellt werden, wenn man bioelektrische Untersuchungen auf der Hirnrinde anstellt (Kornmüller 1932–37). Leider wurde dies auch von Adrian und Matthews nicht in Rechnung gezogen bei ihrem wertvollen Ansatz, eine Analyse des Elektrenkephalogramms auch an Hand von Untersuchungen an Tieren durchzuführen, wobei sie auch Befunde über die Abhängigkeit des Kurvenbildes von der Elektrodenlage bei bioelektrischen Untersuchungen auf der Hirnrinde mitgeteilt haben.

Die unipolare Ableitung hat den Vorteil, dass sie im allgemeinen Schwankungen grösserer Amplitude als die enge bipolare Ableitung ergibt, so dass man leichter oberhalb des Störspiegels der Apparatur arbeiten kann. Ferner hat die unipolare Ableitung den Vorteil, dass es natürlich viel leichter gelingt, eine einzelne Elektrode in ein bestimmtes architektonisches Feld zu legen als zwei Elektroden. Ob diese Ableitungsart den Mangel hat, dass die erhaltenen Kurven nicht nur von der Auflagestelle der differenten Elektrode, sondern auch von dem Gewebe zwischen differenter und indifferenter Elektrode stammen, soll uns hier in erster Linie beschäftigen.

II. Methodik

Die Untersuchungen zur vorliegenden Mitteilung wurden an Kaninchen durchgeführt. Ihre Befunde sind an folgende Voraussetzungen geknüpft:

Die Kopfschwarte und der Knochen sind in einem möglichst grossen Bereiche von den Hirnableitestellen entfernt, und die Dura ist zurückgeschlagen. Es liegt mindestens von einer Hemisphäre nahezu die gesamte dorsale Konvexität frei. Die Ableitungen erfolgen durch Auflegen der Elektroden auf die Hirnrinde und nicht durch Einstechen. Die "indifferente" Elektrode muss tatsächlich frei von elektrischen Potentialschwankungen sein. Sie hat möglichst weit vom Gehirn wie auch von anderem bioelektrisch aktiven Gewebe, z.B. Muskeln, entfernt zu liegen und darf auch keine gut leitenden Verbindungen, z.B. durch Kochsalzlösung, zu solchen Geweben haben.

Des weiteren soll noch auf einige andere methodische Besonderheiten hingewiesen werden:

Zur Ableitung wurden überwiegend die im folgenden beschriebenen Metallelektroden benutzt, die sich durch kontrollierbaren Auflagedruck und durch zuverlässige Kontaktgabe auszeichnen. Siehe *Fig. 1!*

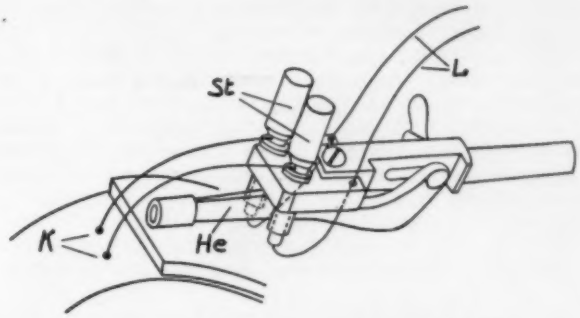

FIG. 1. Metallelektrode. Beschreibung im Text.

Ein mikrometrisch verstellbares Stativ trägt den Elektrodenhalter. Dieser besteht aus einem Vierkanteisen und einer daran festgeschraubten Presstoffplatte, in die zwei Messingbuchsen eingesetzt sind. An ihnen sind die Zuleitungen *L* angelötet. In die Buchsen werden kleine Stecker *St* gesteckt, an denen Messingdrähte von 0,2 mm ϕ angelötet sind, die am freien Ende angeschmolzene Silberkügelchen, *K*, von 1,5 mm ϕ tragen. Von einem galvanischen Überziehen dieser Kugeln, die die eigentlichen Auflageelektroden darstellen, mit AgCl wurde abgesehen, da aus den weiter unten dargelegten Gründen nicht mit der Wirkung von Polarisationsspannungen zu rechnen war, was sich bei den Versuchen durchaus bestätigte. Der Druck, mit dem die sehr weich federnden Messingdrähte die Silberkugeln auf das blossliegende Gehirn anlegen, betrug bei den in Betracht kommenden Durchbiegungen der Drähte ca. 0,1 g. Demnach war der entsprechende Flächendruck bei einer Auflagefläche von 3,5 mm² pro Kugel 0,03 g/mm². Natürlich hängt dieser Druck von dem Grade der Durchbiegung ab. Um nun bei plötzlicher Unruhe des Versuchstieres zu verhindern, dass die Elektroden die Hirnoberfläche verletzen, wurde an dem Elektrodenhalter ein einstellbarer, am Ende mit Gummischlauch überzogener Hebel *He* angebracht, der am Rande der Trepanationsöffnung dem stehengebliebenen Schädelknochen aufliegt, wenn gleichzeitig die Elektroden mit dem zulässigen Druck das freiliegende Gehirn berühren. Bei Unruhe des Tieres wird dann die gesamte Elektrodenanordnung angehoben, ohne dass sich der Druck auf das Gehirn ändert. Da die eigentlichen Elektroden nur durch ihre Stecker mit den Zuleitungen verbunden sind, ist die Auswechslung gegen Elektroden mit anderen Ausmassen oder die Ersetzung von beschädigten Elektroden ohne Zeitverlust möglich.

Als indifferente Elektroden dienten Tonstiefel oder einfache Metallelektroden.

Zur Verstärkung der bioelektrischen Erscheinungen dienten drei C–W-gekoppelte Verstärkersätze des von Tönnies (1935) konstruierten Polyneurographen, vor deren Eingangsstufen drei Differentialverstärker nach Tönnies* geschaltet waren.

Diese Differentialverstärker haben je drei Eingangsklemmen (a, b, E auf Fig. 2) und zwei Ausgangsklemmen, die zum Gitter und zur Kathode der nachfolgenden Verstärkerstufe, d.h. der jeweils ersten Stufe im Polyneurographen, führen. Durch die besondere Schaltung des Differentialverstärkers, die eine modifizierte Gegentaktschaltung darstellt, ist erreicht, dass gemeinsame Aussteuerungen von a und b

* Noch nicht veröffentlicht.

gegenüber E sich mit weniger als 1/1000 in der registrierten Kurve auswirken, verglichen mit einer gleich grossen Aussteuerung zwischen a und b. Dadurch werden aus dem Wechselstromnetz herrührende Störungen, die die mit a und b verbundenen Elektroden praktisch gleichmässig beeinflussen, sehr weitgehend vermindert. Es muss lediglich auf die gute Kontaktgabe der mit E verbundenen Elektrode geachtet werden, die zur Ableitung der Störungen nach der Erde dient. Sie wird im folgenden als *E*-(Erdungs-) Elektrode bezeichnet und ist nicht zu verwechseln mit der "indifferenten" Elektrode der unipolaren Ableitung. Potentialschwankungen unter der E-Elektrode allein wirken sich praktisch nicht auf den Ableitekreis aus, während sich Spannungsschwankungen, die eventuell unter der "indifferenten" Elektrode auftreten, selbstverständlich voll auswirken. Die Klemmen a und b jedes Differentialverstärkers gehen unmittelbar, d.h. ohne zwischengeschaltete Kondensatoren, an die Gitter der zugehörigen Verstärkerröhren, die im übrigen keine leitenden Verbindungen mit den Kathoden, d.h. keine eingebauten Gitterwiderstände haben. Die Aussteuerung der beiden Gitter erfolgt also rein statisch, ohne dass die abgeleiteten Spannungen durch einen Gitterwiderstand belastet werden. Dadurch ist das Fliessen eines Stromes im Ableitekreis unmöglich, so dass auch die Ausbildung von störenden Polarisationsspannungen mit Sicherheit verhindert ist. Die Verwendung von "unpolarisierbaren" Elektroden ist dadurch überflüssig, und deshalb konnten die oben beschriebenen sehr einfach herzustellenden und mechanisch unempfindlichen Metallelektroden ohne Nachteil verwendet werden.

Wird einer der beschriebenen Differentialverstärker zur bipolaren Ableitung benutzt, dann wird die eine der differenten Elektroden mit a und die andere mit b verbunden. Siehe *Fig. 2!* Als E-Elektrode verwenden wir eine grossflächige Klemme an einem Ohr.

Bei der unipolaren Ableitung kann entweder

α) a mit einer differenten und b mit einer indifferenten Elektrode (z.B. auf dem Nasenbein) verbunden werden. Die E-Elektrode des Differentialverstärkers liegt wie eben erwähnt. Oder

β) es wird auf die Trennung der indifferenten von der E-Elektrode verzichtet, d.h. beide werden gemeinsam genommen.

Für die Registrierung der bioelektrischen Spannungen sind die beiden unipolaren Ableitungsarten (α und β) vollkommen gleichwertig; nur für die Ausschaltung der Störungen besteht ein Unterschied, da bei der Schaltung nach β die Gegentaktwirkung aufgehoben und die Störanfälligkeit dadurch erhöht ist.

Für die in Abschnitt *III, 2* dieser Mitteilung beschriebene Versuchsreihe war es nötig, mit den vorhandenen Mitteln eine Schaltung der Verstärker zu finden, die es ermöglicht, eine Kurve zu registrieren, welche die Differenz der Potentialschwankungen von zwei gleichzeitigen unipolaren Ableitungen darstellt. Dies wurde auf folgende Arten erzielt:

1. In der Fig. 2 stellen A, B und C schematisch drei Differentialverstärker dar, deren Eingangsklemmen wieder mit a, b und E bezeichnet sind. Auf dem Gehirn des Versuchstieres liegen die mit 1 und 2 gekennzeichneten differenten Elektroden; auf dem Nasenbein liegt die indifferente Elektrode N. Am Ohr des Tieres ist eine Klemme O befestigt als E-Elektrode. Im Verstärker C wird die Potentialdifferenz zwischen 1 und 2 verstärkt und auf den nachfolgenden Verstärkersatz übertragen; die Elektrode O dient hierbei nur zur Erdung und damit zur Ableitung der aufgenommenen Wechselstromstörungen. Die Elektrode 1 ist mit der Klemme a des Verstärkers A und die Elektrode 2 mit b von B verbunden, deren E-Klemmen gemeinsam mit der von C geerdet sind. Die noch freien Klemmen b von A und a von B sind gemeinsam mit der indifferenten Elektrode N

verbunden. Die Verstärker A und B erhalten also als Aussteuerung die Potentialdifferenz zwischen 1 und N bzw. N und 2 in unipolarer Ableitung. Die in A und B verstärkten Spannungsschwankungen werden gemeinsam auf das Gitter einer nachfolgenden Stufe gegeben. Da A und B hierbei so geschaltet sind, dass eine gemeinsame Spannungsänderung an 1 und 2 sich in dem zusammengeschalteten Ausgang aufhebt, so wirkt an diesem Ausgang tatsächlich die Differenz der unipolaren Ableitung zwischen 1 und N bzw. N und 2 als Aussteuerung.

2. Es können auch hier, wie oben unter β gesagt, die indifferente und die E-Elektrode gemeinsam genommen werden. Siehe die gestrichelte Linie zwischen a und E des Verstärkers B in Fig. 2!

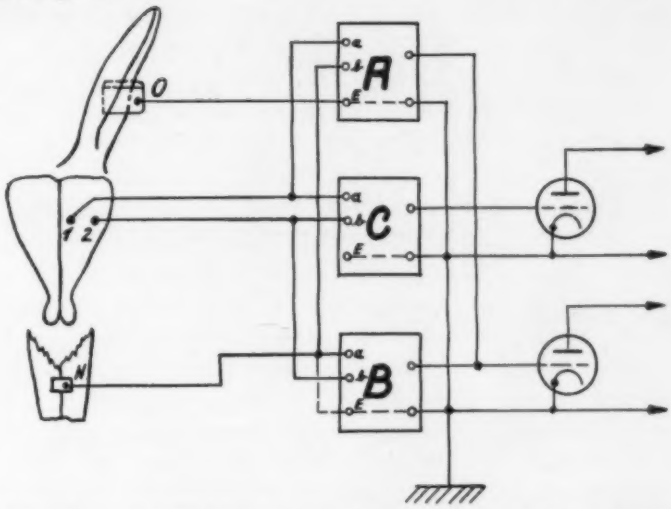

FIG. 2. Links: Lage der Elektroden am Tier. Rechts: Schaltung zur physikalischen Differenzbildung der Kurven von den unipolaren Ableitungen 1—N und 2—N und zur gleichzeitigen Registrierung der bipolaren Ableitung 1—2. Beschreibung im Text.

Die Registrierungen wurden mit den Tintenschreibern des Tönnies'schen Polyneurographen (l.c.) vorgenommen.

Geringfügige Abweichungen in der Aufzeichnung von Frequenzen um 50 Hertz erklären sich aus kleinen, während dieser Untersuchung bestehenden Differenzen zwischen den Dämpfungseigenschaften der einzelnen Schreiber. Diese Abweichungen traten auch auf, wenn eine gemeinsame Aussteuerung auf die drei benutzten Schreiber geschaltet wurde und erwiesen sich bei einer genaueren Durchmessung als physikalisch bedingt. So weit also bei dem Vergleich der elektrisch gewonnenen Differenz zweier unipolarer Ableitungen mit der zugehörigen bipolaren Ableitung derartige geringe Unterschiede auftreten, sind sie nach genauerer physikalischer Analyse durch die erwähnte Verschiedenheit der Schreibereigenschaften auch quantitativ vollkommen erklärt.*

III. ERGEBNISSE

1. Unipolare Ableitungen mit verschiedener Lage der indifferenten Elektrode

Die Hirnstelle 1 wird, wie Fig. 3 zeigt, unipolar gleichzeitig I gegen die Protuberantia occipitalis externa (P) und II gegen das Stirnbein (S) abgeleitet.

* Einzelheiten über die Frequenzeigenschaften der für die vorliegende Untersuchung benutzten Registrierung wird Schaeder demnächst im Rahmen einer Mitteilung über die Aufzeichnungsmethoden bioelektrischer Erscheinungen mit besonderer Berücksichtigung der Tintenschreibung angeben.

Diese beiden Kurven (I und II) sind erstaunlich parallel, und jede Einzelheit der einen Kurve ist auch an der anderen zu sehen. Das ist umso bemerkenswerter, als sich bei den Ableitungen für Kurve I und II morphologisch und entsprechend auch bioelektrisch unterschiedliche Hirngebiete zwischen dem gemeinsamen differenten und den verschiedenen indifferenten Punkten befinden. Dies soll die gleichzeitig registrierte Kurve III, eine bipolare Ableitung von der Area praecentralis granularis (2–3 in

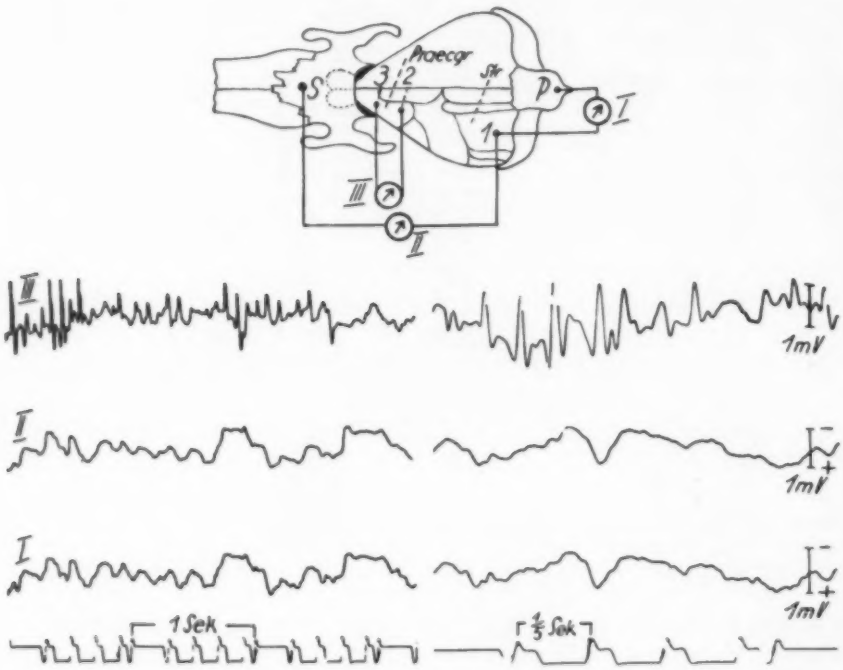

Fig. 3. Oben: Grosshirn und Teile des knöchernen Schädels eines Kaninchens, von oben gesehen. Auf der linken Hemisphäre schematisch die architektonische Rindengliederung.

Unten: Gleichzeitige Ableitung von

I: 1–P
II: 1–S
III: 2–3

Praecgr), zeigen. Das genannte Feld, dessen Eigenströme u.a. durch Gruppen rascher Schwankungen (12–15 Hz) gekennzeichnet sind, liegt breit übcr der Verbindungslinie der Punkte 1 und S, also zwischen den Ableiteelektroden der Kurve II. Trotzdem lässt die Kurve II nichts von diesem raschen Rhythmus erkennen.

Nach dem in *Fig. 3* dargestellten Prinzip wurde unter Beibehaltung der angegebenen Lagen für die indifferenten Elektroden unipolar über den verschiedensten Stellen der Hirnrinde abgeleitet. Dieses Material führte zu dem gleichen Befunde, wie das angegebene Beispiel, nämlich:

Die Kurvenform der unipolaren Registrierungen der bioelektrischen Erscheinungen je einer Hirnrindenstelle ist unabhängig von der Lage der indifferenten Elektrode.

2. Gleichzeitige unipolare und bipolare Ableitungen von zwei Rindenstellen

Von den Hirnrindenstellen 1 und 2 der Fig. 4 wird gleichzeitig folgendermassenabgeleitet (siehe A der Fig. 4): I zwischen 1 und 2, II zwischen 2 und der Protuberantia occipitalis externa (P) und III zwischen 1 und Nasenbein (N). Wenn sich auf den Ableitekreis tatsächlich nur die Potentialschwankungen auswirken sollten, die in unmittelbarer Nähe der Elektroden auftreten und nicht die bioelektrisch aktiven Gebiete zwischen den Elektroden, dann müsste die Kurve der bipolaren Ableitung (1–2) gleich sein der Differenz* der beiden unipolaren Registrierungen (1–N und 2–P). Es wurden in diesem Falle mit Absicht für die beiden unipolaren Ableitungen verschiedene indifferente Elektrodenlagen (N und P) gewählt, damit die bioelektrisch aktiven Gebiete zwischen den Elektrodenpaaren der unipolaren Ableitungen verschieden sind. Nur so lässt sich mit Bestimmtheit die Frage beantworten, ob die bipolare Ableitung gleich ist der Differenz der beiden unipolaren Ableitungen. Andernfalls nämlich könnte sich eine gemeinsame Strecke zwischen den Elektrodenpaaren der unipolaren Ableitungen zufolge einer gemeinsamen indifferenten Elektrode vorfinden und die Subtraktion gleicher Einwirkungen auf beide unipolare Ableitekreise würde die bipolare Ableitung ergeben, obgleich sich in diesen Fällen das zwischen den differenten Stellen und dem gemeinsamen indifferenten Punkt liegende Gewebe doch auf den Ableitekreis auswirken könnte. Die Differenz zwischen den Potentialschwankungen zweier verschiedener Ableitungen wurde in der im methodischen Teil dargelegten Weise direkt ermittelt. Siehe Fig. 2! Das Ergebnis zeigen die Streifen B und C der Fig. 4. B I und C I stellen bipolare Registrierungen zwischen den Punkten 1 und 2 dar. Die Kurven B, III–II und C, III–II sind die Differenzen zwischen den Potentialschwankungen der unipolaren Ableitungen 1–N und 2–P. Die Figur zeigt deutlich, dass die Kurvenform der bipolaren Ableitung (I) gleich ist den Kurven, die die Differenz der beiden unipolaren Ableitungen (III–II) darstellen. Es muss ausdrücklich bemerkt werden, dass alle Kontrollmöglichkeiten erschöpft wurden, die die Unabhängigkeit der bipolaren Ableitung von den Ableitungen der Differenzkurven erwiesen.

Ausser auf diesem physikalischen Wege wurden auch geometrische Subtraktionen von gleichzeitig registrierten unipolaren Kurven vorgenommen. Die so konstruierte Kurve war immer und für alle Einzelheiten völlig identisch mit der gleichzeitig registrierten bipolaren Kurve. Da letztere Kurve keine zusätzlichen Schwankungen aufweist, lässt sich auch aus dieser Versuchsreihe folgern, dass sich das Gewebe zwischen den Elektroden nicht

* Die Polaritäten sind an den Eichstrichen ersichtlich

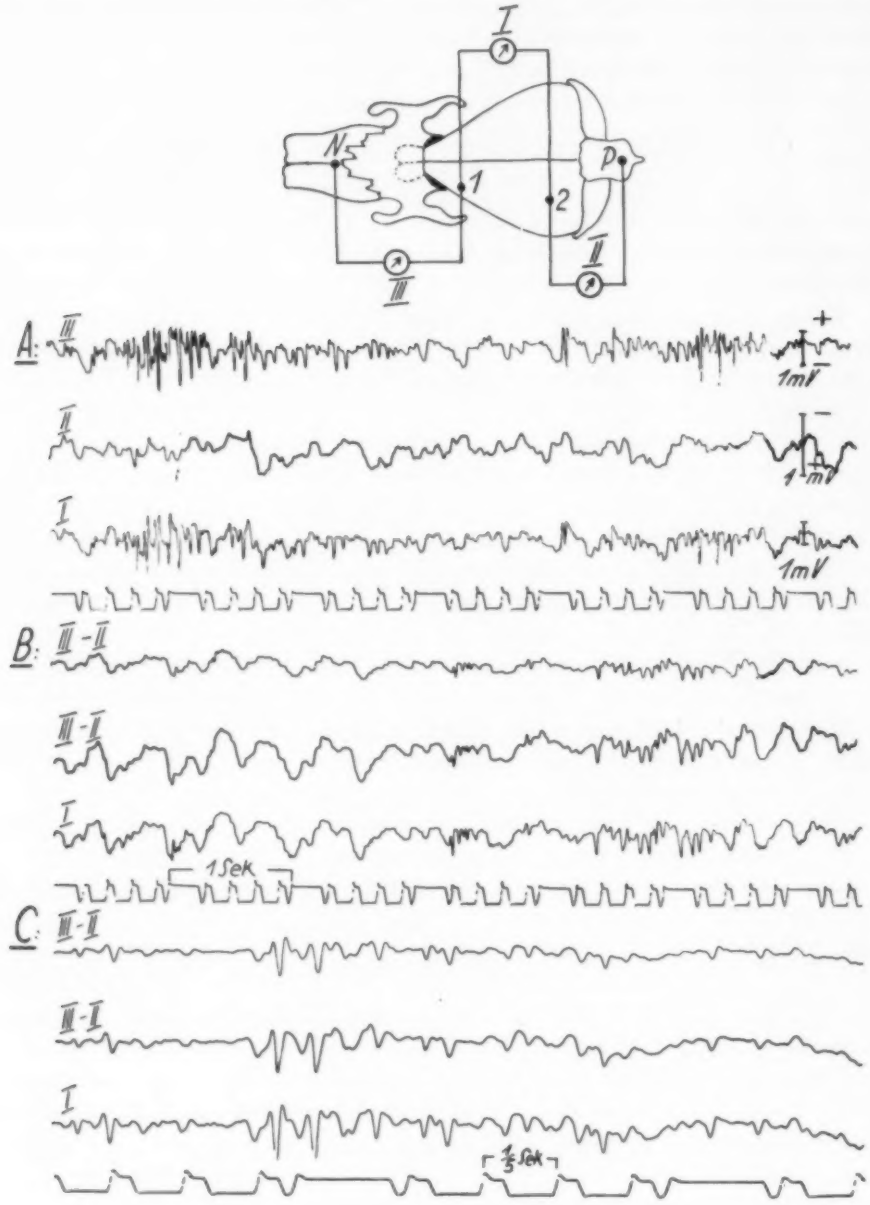

FIG. 4. Gleichzeitige Ableitung von

A:

I: 1–2
II: 2–P
III: 1–N

B und C:

I: 1–2
III–II: Differenz von (1–N) und (2–P)

merkbar auf den Ableitekreis auswirkt. Dass dies selbstverständlich nur unter den in der Methodik aufgezeigten Voraussetzungen gilt, brauchte nicht noch einmal hervorgehoben zu werden.

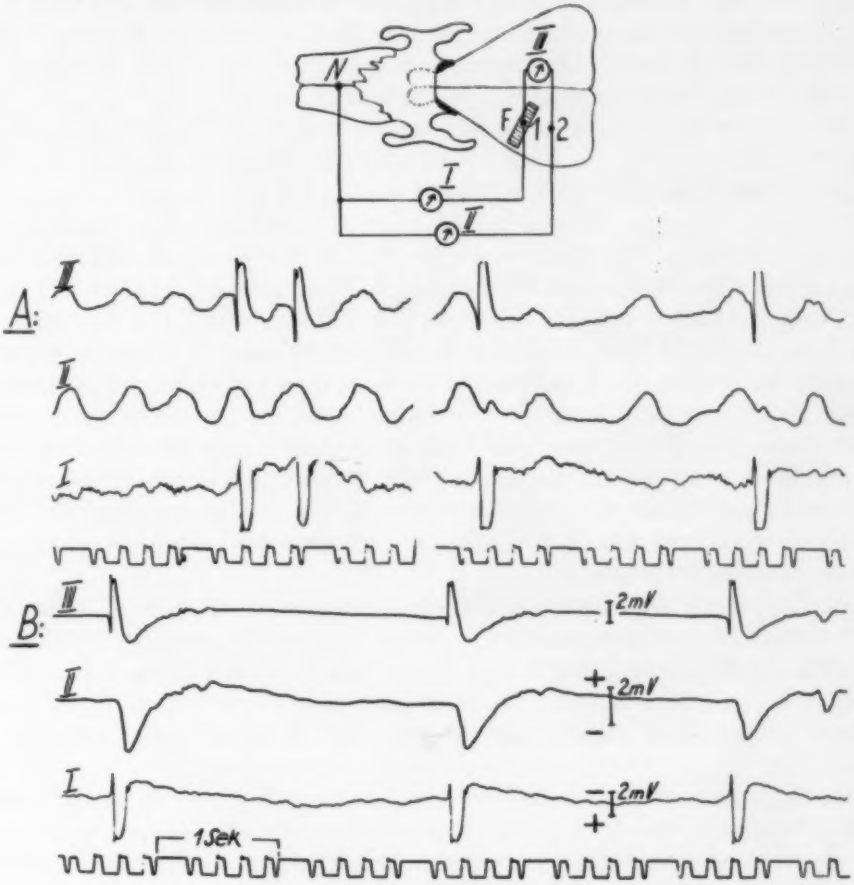

FIG. 5. Gleichzeitige Ableitung von
I: 1–N
II: 2–N
III: 1–2
F = Filtrierpapier mit Strychnin.

3. *Abnorm starke bioelektrische Potentialschwankungen (Krampfströme) auf der Strecke zwischen den Elektroden*

Es wurde die in Fig. 5 (oben) dargestellte Elektrodenanordnung benutzt. Nach Strychninisation der Stelle 1 wurde von 1 und 2 gleichzeitig sowohl bipolar (A III) als auch von jedem einzelnen Punkte unipolar gegen das Nasenbein (N) abgeleitet: A I = 1 − N und A II = 2 − N. Alle Elektrodenauflagepunkte liegen auf einer Geraden. Die Krampfstromzacken über 1 sind nur auf der unipolaren Ableitung von Stelle 1 (A I) und auf der bipolaren

Ableitung 1–2 (A III) festzustellen. Die unipolare Ableitung von 2 (A II) lässt nichts von Krampfstromzacken erkennen, obgleich sie unweit davon und noch dazu zwischen den Elektroden vorhanden sind. Bei dieser Versuchsreihe wurden bei den einzelnen Tieren verschiedene Rindenstellen zwischen 2 und dem Nasenbein (N) strychninisiert, so dass die Gegenden mit Krampfströmen in den verschiedensten Abständen von den Punkten 2 und N lagen. Auf Streifen B der *Fig. 5* kommen wir weiter unten zu sprechen.

Es wurden auch noch Abänderungen dieser Versuchsanordnung durchgeführt, z.B. folgende, die in Fig. 6 dargestellt ist: Es liegt je eine Elektrode auf dem Nasenbein (N), auf der Area praecentralis granularis (1), auf der Area striata (2) und auf der Protuberantia occipitalis externa (P). Nach einer Kontrollregistrierung und Strychninisation mittels eines Blättchens Filtrierpapier (F) von 2 wird I zwischen 1 und 2, II zwischen 2 und N und III zwischen 1 und P abgeleitet. Die Kurven I und II zeigen deutliche Krampfstromentladungen, Kurve III dagegen nicht, obgleich auch hier die Krampfstromentladungen zwischen den Elektroden dieser Ableitung sehr intensiv vorhanden sind. Nebenbei bemerkt zeigen diese dreifachen Registrierungen auch sehr schön, dass die bipolare Kurve (I) alle Wellen der beiden unipolaren, aber keine zusätzlichen Schwankungen erkennen lässt. Schon die grobe Betrachtung lässt erkennen, dass die Kurve der bipolaren Registrierung gleich ist der Differenz der beiden entsprechenden unipolaren Registrierungen.

In Ergänzung der Befunde der eben geschilderten Versuchsreihe muss noch darauf hingewiesen werden, dass nach länger dauernder Strychnineinwirkung auf die Stelle 1 der Fig. 5 und auf die Stelle 2 der Fig. 6 sich auch von den nicht strychninisierten differenten Ableitepunkten Krampfströme gelegentlich registrieren lassen. Ein Beispiel dafür zeigt B der Fig. 5:

Im Gegensatz zu A enthält hier die Ableitung II ebenfalls Krampfstromschwankungen. Diese aber haben eine andere Form als die der Ableitung I. Sie sind träger und weisen ausserdem bei grösserer Papiergeschwindigkeit eine deutliche Latenzzeit gegenüber den Krampfstromschwankungen von I auf. Die Latenzzeit betrug etwa 75 σ. Der Abstand zwischen den Punkten 1 und 2 betrug 8 mm, das würde in diesem Falle eine Leitungsgeschwindigkeit von knapp über 100 mm pro Sekunde bedeuten. Es handelt sich hier also nicht um eine physikalische Streuung der grossen Potentialschwankungen der Stelle 1 auf die Elektrode der Stelle 2, sondern darum, dass sich die von Stelle 1 ausgehenden Erregungen auf Stelle 2 auswirken. Die Registrierung B III, die die gleichzeitig vorgenommene bipolare Ableitung darstellt, setzt sich aus den aufeinanderfolgenden Krampfstromschwankungen der beiden unipolaren Ableitungen I und II zusammen. Man wird, wenn man quantitative Unterschiede ausser Acht lässt, bei diesem Kurvenbild an das Verhalten der bipolaren Ableitung von Muskeln bzw. peripheren Nerven erinnert.

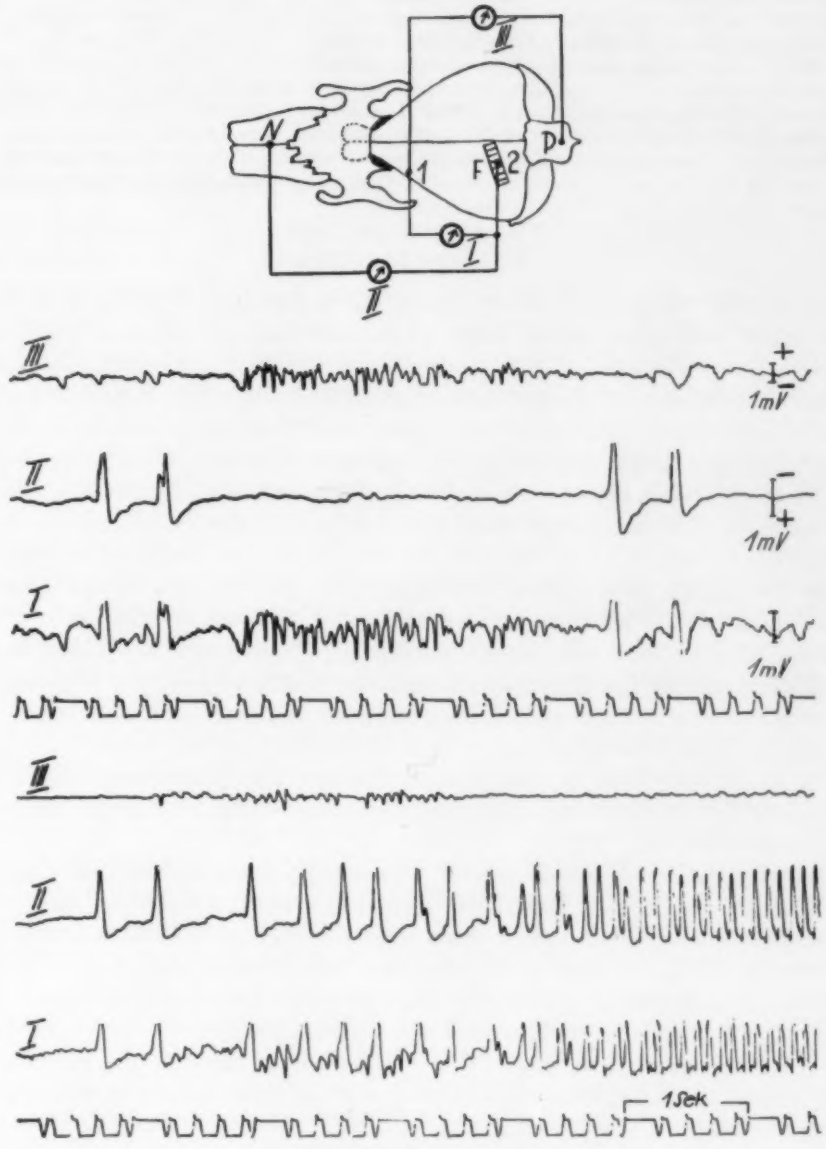

FIG. 6. Gleichzeitige Ableitung von
I: 1–2
II: 2–N
III: 1–P
F = Filtrierpapier mit Strychnin.

Die Erregungsausbreitung auf der Hirnrinde liess sich auf Grund der normalen Erscheinungen (Eigenströme) bisher nur in vereinzelten geeigneten Fällen feststellen (Kornmüller, z.B. 1933 und 1935(a)), weil es bei der Mannigfaltigkeit der ständig vorhandenen Potentialschwankungen oft schwer fällt, einander entsprechende Wellen verschiedener Ableitepunkte genau zu ermitteln. Kornmüller hat (1937(a)) kurz darauf hinweisen können, dass die transkortikale Ausbreitung abnorm starker Erregungen, wie sie sich wohl in den Krampfströmen anzeigen, in den differenten Rindenarealen verschieden sein kann und offenbar von den morphologischen Verbindungen tangentialer Richtung innerhalb der Hirnrinde abhängig ist. Inzwischen hat Adrian der Frage der Erregungsausbreitung über der Hirnrinde eine besondere Untersuchung gewidmet, in welcher er zu bemerkenswerten Befunden gekommen ist, deren Mitteilung in diesem Zusammenhang zu weit führen würde.

IV. Besprechung

Die hier mitgeteilten Befunde sind unseres Erachtens eindeutig und klar, wenn auch eine Ermittlung ihrer physikalischen Grundlagen noch nicht vorgenommen worden ist. Wir unterlassen es, hier diesbezügliche Auffassungen auszusprechen. Wenn diese Ergebnisse auch einigen Autoren selbstverständlich sein mögen, so ist uns andererseits bekannt, dass selbst manche Elektrobiologen sie nicht erwartet hätten. So ist z.B. an der unipolaren Ableitung vielfach Kritik geübt worden. Siehe die Einleitung! Nach den mitgeteilten Befunden ist aber sicher, dass die unipolare Rindenableitung vor der bipolaren entschieden Vorteile hat und dass die einleitend ausgesprochenen Bedenken gegen diese Ableitungsart nicht zu Recht bestehen. Trotzdem sind wir weiterhin der Auffassung, dass es zweckmässig ist, bei Untersuchungen über die bioelektrischen Erscheinungen des Gehirns nach Möglichkeit sowohl die unipolare als auch die bipolare Ableitung vorzunehmen (Kornmüller 1937(b)). Dies geschieht am besten durch gleichzeitige mehrfache Registrierungen. Auf Grund eines solchen Materials wird man in der Analyse der bioelektrischen Erscheinungen des Gehirns voraussichtlich leichter weiterkommen als auf Grund nur einer der beiden Ableitungsarten.

Die mitgeteilten Befunde gelten, wie gesagt, nur für den Fall, dass vom weit freigelegten Gehirn registriert wird. Die Ableitungen vom blossliegenden Gehirn sind aber unter allen Umständen viel mehr in der Lage, über das tatsächliche und unverfälschte bioelektrische Verhalten der Hirnrinde etwas auszusagen als Untersuchungen, bei denen durch die Kopfschwarte und den Knochen registriert wird. So ist anzunehmen, dass bei Registrierungen durch den uneröffneten Schädel die oben mitgeteilten eindeutigen Ergebnisse nicht zu gewinnen sind. Dieses zu prüfen, muss einer gesonderten Versuchsreihe vorbehalten bleiben. Keinesfalls aber ist es angängig, auf Grund von Befunden, die durch Ableitung vom uneröffneten Schädel gewonnen wurden, Ergebnisse zu bezweifeln, die durch direkte Rindenableitungen in jahrelangen Untersuchungen von verschiedenen Autoren immer wieder bestätigt wurden.

Berger schreibt z.B.: "Nun haben aber die schönen Versuche Ectors' ergeben, dass man auch beim Kaninchen unter der Einwirkung der verschiedensten Sinnesreize bei einer bipolaren Ableitung von der Rinde selbst mit 4–5 mm voneinander entfernten

Elektroden, und zwar im Bereich des zugehörigen Sinneszentrums keine Spannungszunahme der Potentialschwankungen, sondern dabei, wie ich es schon 1930 beim Menschen beschrieben habe, einen Spannungsabfall findet, indem die grossen α−W. schwinden und durch kleinere kurze β−W. ersetzt werden." Wir bezweifeln nicht diesen Befund von Ectors, der nicht vom weit blossliegenden Gehirn gewonnen wurde, sprechen ihm aber völlig die Fähigkeit ab, die unzweifelhafte Tatsache zu widerlegen, dass bei direkter und morphologisch kontrollierter Ableitung von der Area striata sowohl bei unipolarer als auch bei bipolarer Elektrodenanordnung auf Augenbelichtung Steigerungen der bioelektrischen Spannungsproduktion im Sinne der Feldaktionsströme zu finden sind. Das gleiche gilt für die beschriebenen Areale, die auf andere Qualitäten von Sinnesreizen Aktionsströme produzieren.

So lange daher die besonderen physikalischen Verhältnisse der Ableitungen durch den uneröffneten Schädel (Berger) nicht restlos geklärt sind, erscheint es uns unberechtigt, die Ergebnisse der Untersuchungen über den Berger-Rhythmus mit denen der bioelektrischen Lokalisationsmethodik (Kornmüller 1932–1937) zu vermischen bzw. Befunden der direkten Hirnableitung entgegenzustellen, weil Ableitungen durch den Schädel nicht Gleiches ergeben haben. Andererseits sind wir aber davon überzeugt, dass sich in absehbarer Zeit Klarheit über das Verhältnis der bioelektrischen Bilder, die einerseits durch direkte Rindenableitung und andererseits vom uneröffneten Schädel gewonnen werden, ergeben wird.

Es muss noch ausdrücklich bemerkt werden, dass die oben mitgeteilten Befunde nur für das lebende Hirngewebe gelten und nicht für Hirnteile, die tot (nekrotisch) sind oder teilweise grobe Schädigungen aufweisen. Vereinzelte Befunde, deren systematische Nachprüfung noch aussteht, veranlassen zu dieser Feststellung.

Ausserdem gilt das oben Mitgeteilte, weil nur dieses untersucht wurde, für die Grössenordnung der bioelektrischen Erscheinungen der Hirnrinde und für die zu deren Registrierung üblichen Empfindlichkeiten der Apparate. Selbstverständlich ist anzunehmen, dass sich grössere Spannungen als die genannten auch auf Elektroden, die in weiterer Entfernung liegen, auswirken, und schliesslich muss auch mit entsprechend grossen Empfindlichkeiten, die aber bei dem üblichen Versuch praktisch nicht gebraucht werden, eine Streuung entfernter liegender Punkte auf die Elektroden feststellbar sein. So haben Untersuchungen von Jung und Kornmüller, welche gleichzeitige mehrfache Ableitungen bioelektrischer Erscheinungen subkortikaler Kerne betreffen, wie an anderer Stelle ausgeführt wird*, unter Umständen abweichende Befunde ergeben, was u.a. darauf zurückzuführen ist, dass die Grössenordnung der bioelektrischen Potentialschwankungen subkortikaler Kerne niedriger liegt als die der Hirnrinde.

V. Zusammenfassung

Bei Ableitung von der weit blossliegenden Hirnrinde ist

1. das Kurvenbild der unipolaren Ableitungen unabhängig von der Lage

* Erste Mitteilungen darüber erscheinen im *Zbl. Neurol.* (Vortrag in der Neurol.-Psychiatr. Ges. Berlin, Jan. 1938) und im *Arch. Psychiatr.*, 1938, *108*.

der indifferenten Elektrode, obgleich bei verschiedener Lage dieser Elektrode morphologisch wie bioelektrisch unterschiedliche Hirngebiete zwischen den Ableitepunkten liegen.

2. Das Kurvenbild der bipolaren Ableitung ist gleich der Differenz der beiden unipolaren Kurven, die von den Punkten der bipolaren Ableitung gewonnen werden.

3. Selbst Krampfströme, die z w i s c h e n den beiden Elektroden einer Ableitung hervorgerufen werden, lassen unter den üblichen Bedingungen keine physikalische Streuung auf diese Elektroden erkennen.

Am Schluss werden die Befunde kurz besprochen.

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THE INFLUENCE OF HYPOGLYCEMIA ON THE SENSITIVITY OF THE CENTRAL NERVOUS SYSTEM TO OXYGEN WANT*

ERNST GELLHORN, R. C. INGRAHAM, AND L. MOLDAVSKY†
Departments of Physiology and Psychiatry, College of Medicine, University of Illinois, Chicago

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I. INTRODUCTION

IN AN earlier paper by Glickman and Gellhorn (1938) it was shown that rats when in hypoglycemia show an increased sensitivity to diminished barometric pressure. A mild degree of anoxia, which produces no symptoms at normal blood sugar levels, decreases the latent period for insulin convulsions, although the blood sugar at the time of convulsions is no lower than that associated with insulin convulsions in animals kept under normal atmospheric pressure. The experiments give added support to the anoxia theory of insulin convulsions. It is important to extend the observations to preconvulsive states in order to determine whether a subconvulsive lowering of the blood sugar is also accompanied by an increased sensitivity to low oxygen tensions. If this were the case substantial progress would be made in the understanding of the mechanism by which hypoglycemia affects the central nervous system. In order to test this hypothesis it is desirable to use a reaction, suitable for quantitative measurements, and one that is also dependent on the excitability of some part of the central nervous system. For this purpose the blood pressure response to low oxygen tension was chosen. Gasser and Loevenhart (1914), and later Heymans, Nowak and Samaan (1934) concluded that the rise in blood pressure accompanying the inhalation of air at a low oxygen tension is due to direct stimulation of the vasomotor center. Since the level of the blood pressure increases with decreasing oxygen tension, this reaction may be used for quantitative study. Recent experiments of Lambert and Gellhorn (1938), however, indicate that the rise in blood pressure during anoxia is due to *reflex* stimulation of the vasomotor center. For our considerations this new interpretation of the blood pressure rise occurring in anoxia is of little concern since the rise in blood pressure may be taken as a measure of sympathetic excitation, irrespective of whether the sympathetic center has been stimulated directly or reflexly. If the theory based on the work of Olmsted and Logan (1923), Olmsted and Taylor (1924), Holmes (1930), Wortis (1935), Dameshek and Myerson (1935), Loman and Myerson (1936), and Himwich and collaborators (1937) is correct, that a lowering of the blood sugar reduces both the sugar and oxygen con-

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† The material here presented has been abstracted in two preliminary papers by Moldavsky and Gellhorn (1937) and Ingraham, Moldavsky and Gellhorn (1937).

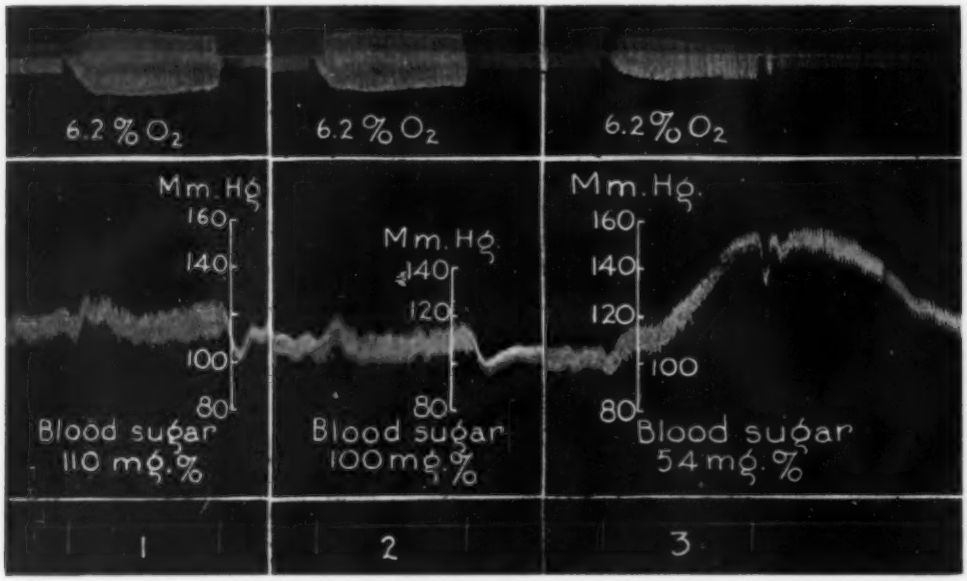
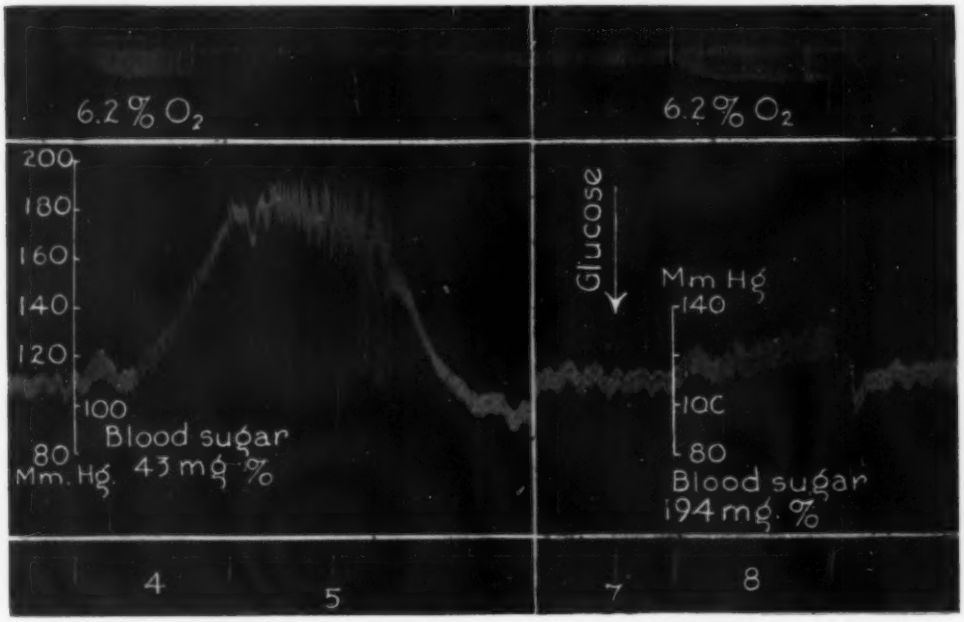


FIG. 1A. In this and the other figures are recorded from above downward: (i) respiration, (ii) blood pressure, (iii) period of 6.2 per cent oxygen inhalation (3 min.). Dog under intraperitoneal sodium amytal anesthesia, 65 mg. per kilo body weight. The amount of insulin injected intravenously varied between 2 and 8 units per kilo. Glucose, levulose, and galactose were injected intravenously either in isotonic or hypertonic solutions. The blood sugar was determined as glucose.



B. Continuation of same experiment, see text.

sumption of the brain, the rate of oxidation in the brain should be diminished to such an extent that a condition prevails comparable to that induced by inhalation of low oxygen tensions. If this were the case, lowering of the blood sugar during a mild degree of oxygen deficiency would induce symptoms of more severe anoxia (as measured in terms of blood pressure response) than would occur at normal blood sugar levels. This would mean, in other words, that as the blood sugar level progressively falls the increment of rise in the blood pressure from inhalation of a given oxygen tension would steadily increase. This indeed has proved to be the case.

EXPERIMENTAL METHODS

Dogs anesthetized by intraperitoneal injection of sodium barbital, sodium amytal, or "Chloralosane" were used as experimental subjects. Blood pressures were recorded from the carotid artery by mercury manometer. The femoral artery and vein of one leg were utilized for withdrawal of samples of blood; Lilly's insulin and the various sugar solutions employed were administered by the intravenous route. The dosages of insulin varied from 1.8 units per kilo to 8 units per kilo. Blood sugar determinations were done on protein free filtrates by the methods of Folin and Wu, or by that of Shaffer and Hartman. Determinations of calcium (Kramer and Tisdall), potassium (Kramer and Tisdall), and phosphorus (Kuttner and Lichtenstein; *cf.*, Peters and Van Slyke, 1931) were also made. The pH was determined with the quinhydrone electrode. The dogs were caused to breathe 6.2 per cent oxygen mixed with nitrogen from Douglas bags for 1–3 minutes. This concentration produces, in ordinary circumstances, either no rise in blood pressure or a slight rise. In some experiments pneumothorax was induced and artificial respiration instituted. More than 60 experiments were performed.

II. Results

1. *Augmentation of blood pressure response to oxygen deficiency during hypoglycemia, and its diminution by glucose*

Figures 1A and B show the alteration in the blood pressure response to the inhalation of 6.2 per cent oxygen as the level of the blood sugar is diminished. It is seen that the blood pressure response to 6.2 per cent oxygen is very slight and practically identical when the blood sugar is 110 and 100 mg. per cent respectively. When insulin becomes effective and tests are made with blood sugar at 54 and at 43 mg. per cent enormous elevations of the blood pressure occur (Figs. 1A and 1B). In the latter experiment the change in pressure is so great that distinct vagal pulses develop; the rise in blood pressure, moreover, continues over a considerable period after air had been readmitted. Even in such circumstances the reaction is completely reversible, as the last tracing in Fig. 1B indicates. The intravenous injection of glucose, by which the blood sugar was raised to 194 mg. per cent, restores the original slight response to 6.2 per cent oxygen. A further increase in blood sugar above the normal level, even up to 400 or 500 mg. per cent, did not alter the blood pressure reaction to 6.2 per cent oxygen.

2. *The reversal of the blood pressure response to low oxygen tensions in hypoglycemia by different monosaccharides*

Investigations of the relative abilities of the various sugars to combat the hypoglycemic state (Herring, Irving and MacLeod, 1924; Noble and

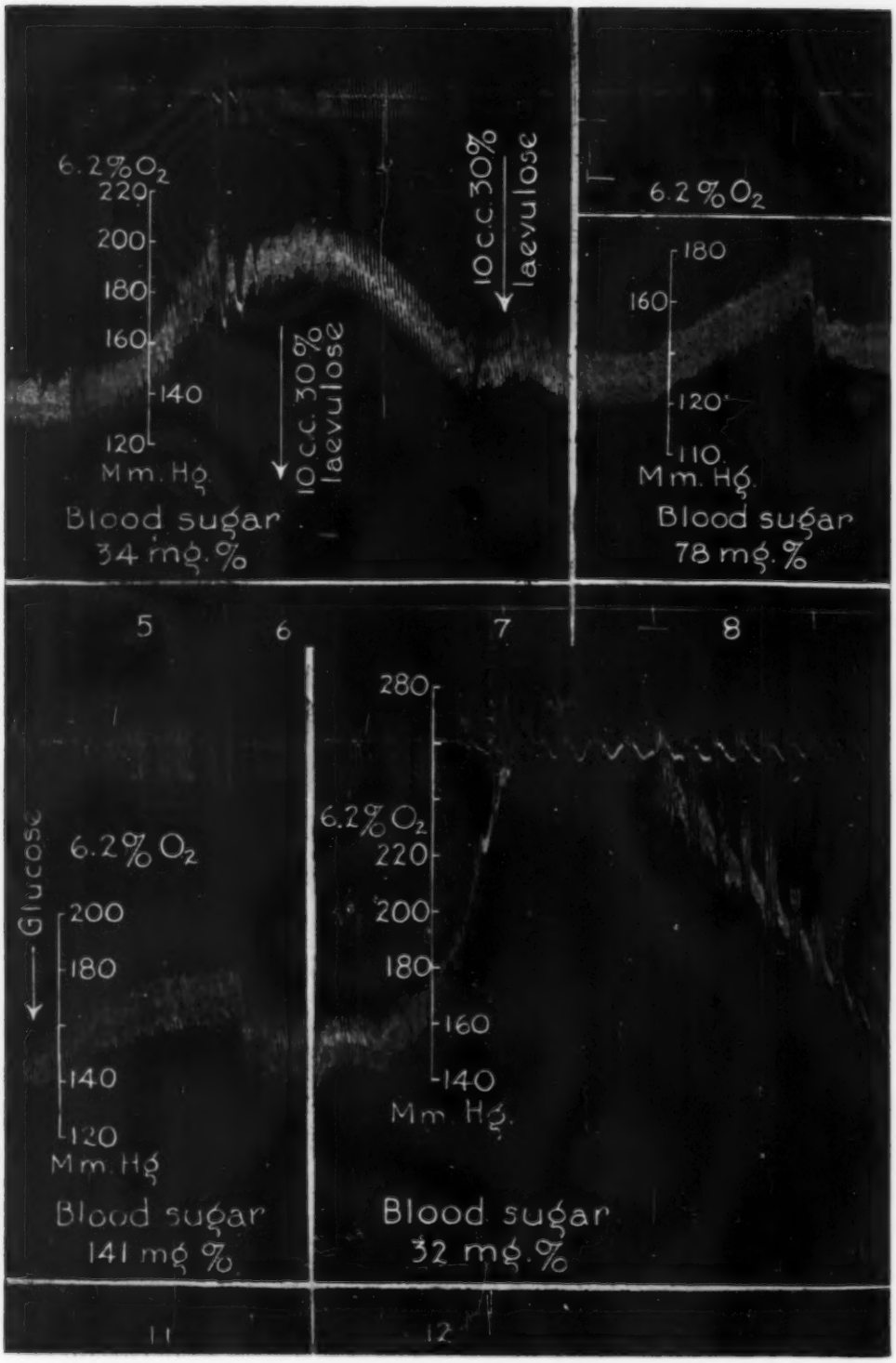


FIG. 2. See text and legend to Fig. 1.

MacLeod, 1923) have shown glucose to be by far the most efficacious. Fructose has a temporary effect and galactose is exceedingly evanescent in its action and then only in mild hypoglycemia. These findings, together with the fact that the blood pressure response to 6.2 per cent oxygen offers a definite insight into the metabolic activities of the brain, led to experiments in which not only glucose, but galactose and fructose were used in attempting to reverse the augmented blood pressure response to oxygen deficiency during hypoglycemia.

Figure 2 indicates that *levulose* has some effect on the blood pressure reaction to inhalation of 6.2 per cent oxygen, since a rise in blood sugar by levulose to 78 mg. per cent (determined as glucose), somewhat lowers the blood pressure response to 6.2 per cent oxygen. Added reduction occurred when a further elevation of the blood sugar level was brought about by injection of glucose. Figure 2 also shows that, even after the sugar had been raised to 141 mg. per cent and a reaction obtained similar to that at normal blood sugar level, the blood sugar began to fall again to 32 mg. per cent causing the blood pressure response to become enormously increased. Since the blood sugar concentration at No. 5 and No. 12 of Fig. 2 were practically identical (34 and 32 mg. per cent respectively) the much greater response at No. 12 indicates that the duration of hypoglycemia is, in addition to the degree of hypoglycemia, an important factor in determining the extent of the blood pressure response.

In general it was found that when the blood sugar was raised to 100 mg. per cent or above by the injection of *levulose* the blood pressure reaction to 6.2 per cent oxygen was not reduced as quickly and as effectively as in similar circumstances when glucose was injected. In some cases, however (*cf.*, the second experiment in Table I), a complete restoration of the original reaction was brought about by levulose.

Galactose was also tested in a number of experiments and was invariably found to be ineffective. In Figs. 3 and 4 typical records are given. In each of these experiments a restoration of the original reaction could be obtained by injection of glucose.

3. *Observations on respiration*

During the experiments described above it was frequently observed that after the period of inhalation of 6.2 per cent oxygen Cheyne-Stokes breathing occurred. Such periodic breathing, however, was generally absent as long as the blood sugar was high. If, however, the blood sugar fell below a critical level, which was ordinarily around 40 mg. per cent, Cheyne-Stokes breathing occurred immediately after the inhalation of 6.2 per cent oxygen and readmission of air. Figure 2 well illustrates this phenomenon, particularly at No. 12 where a prolonged interval of periodic breathing occurs at a blood sugar level of 32 mg. per cent, but even at that level the breathing was perfectly regular before 6 2 per cent oxygen was inhaled. In the same experiment a slight indication of periodic breathing was observed in Fig. 2 at No. 5, but this was

Table I. Ability of Fructose to Reverse the Hypoglycemic Blood Pressure Response to 6.2 Per Cent Oxygen.

Time	Blood sugar mgm. %	Blood pressure in mm. of Hg.		Difference in mm.	Remarks
		Before 6.2% O_2	Max. rise during 6.2% O_2		
11:15 A.M.	90	121	148	27	15 kilo dog injected* with 60 mg./kilo of amytal at 9:00 A.M. Insulin (120 units) injected intravenously at 10:35 A.M.
12:10 P.M.	43.7	110	148	38	Fructose (15 cc. of 30%) injected at 12:15 P.M.
12:23 P.M.	104	106	124	18	
12:51 P.M.	42	122	160	38	
					Another experiment: 16.6 kilo dog injected with 65 mg./kilo amytal at 9:00 A.M. Insulin 8 units/kg. injected between 10:55 and 11:03.
11:36 A.M.	72	98	120	22	
11:57 A.M.	48	101	151	49	15 cc. fructose injected between 12:18 and 12:21 P.M.
12:26 P.M.	102	110	147	37	
12:43 P.M.	64	102	149	47	
					Another experiment: 15.0 kilo dog injected with 65 mg./kilo amytal at 9:00 A.M. Chest opened; artificial respiration. Insulin 8 units/kg. injected bewteen 10:30 and 10:35 A.M.
11:12 A.M.	90	122	148	26	
12:07 P.M.	43.7	109	149	40	15 cc. fructose injected at 12:15 P.M.
12:23 P.M.	104	102	123	21	
1:00 P.M.	42	122	160	38	

* An injection intravenous; anesthesia sodium amytal in all three experiments.

eliminated by the injection of levulose and glucose. A pertinent illustration is also found in Fig. 3, where marked periodic breathing occurred at 44 mg. per cent blood sugar level after the inhalation of 6 per cent oxygen. It is interesting that the injection of galactose which did not alter the blood pressure response to 6.2 per cent oxygen decidedly improved respiration and diminished the period during which periodic breathing was observed (Fig. 3, No. 7).

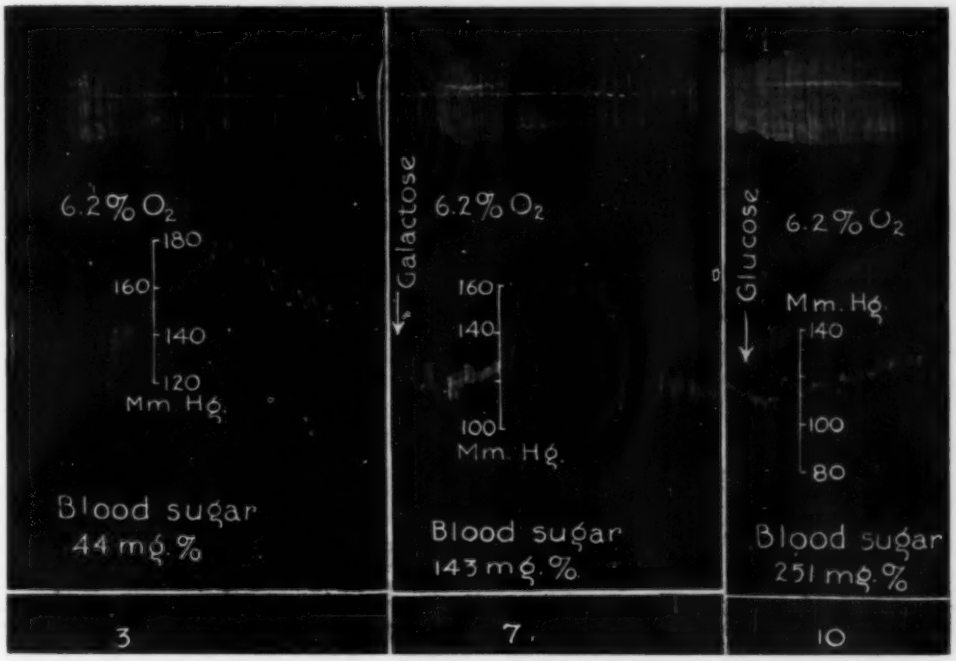


FIG. 3. See text and legend to Fig. 2.

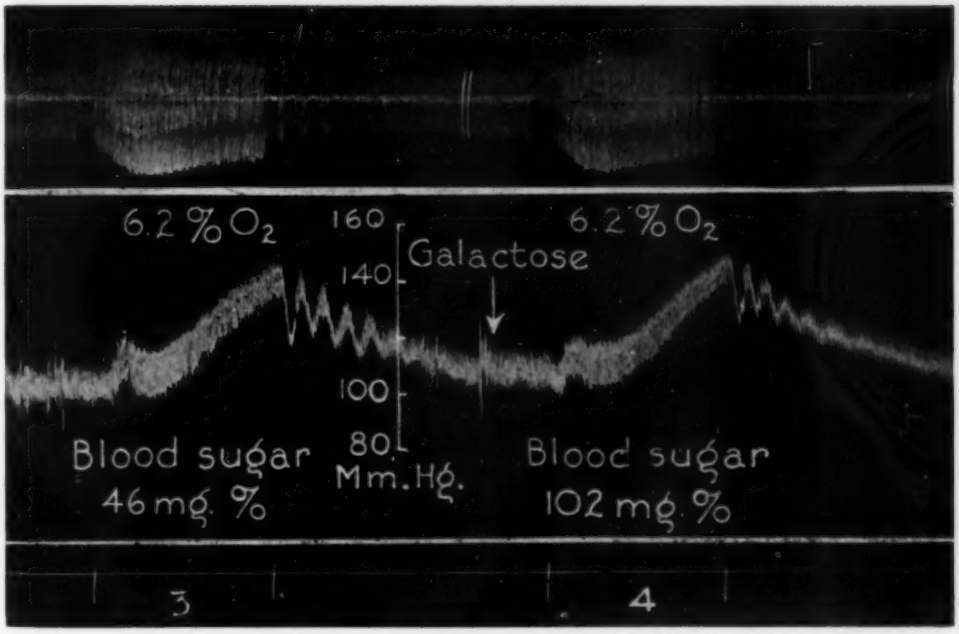


FIG. 4. A further observation on the effects of galactose; see text and legend to Fig. 1.

A further improvement was obtained on injection of glucose (Fig. 3, No. 10). Occasionally it was found that 6.2 per cent oxygen induced a prolonged period of apnea when inhaled at a low blood sugar level. In one experiment the period of apnea lasted for 9 minutes, although before and after this experiment when the blood sugar was higher the respiration was normal. During this long period of apnea it was necessary to resort to artificial respiration to maintain life.

4. *Ionic changes in the blood during insulin hypoglycemia*

The studies described in this paper have included also an investigation of the concentration of those ions in the blood which influence the excitability of the nervous system. The 9 experiments in which such chemical analyses were made are summarized in Table II. The results indicate great variability in the changes of calcium and potassium, these occurring independently of

Table II. Changes in Blood Chemistry after Insulin.

Insulin units per kg.	K mg. %		Ca mg. %		K/Ca ratio		P mg. %		pH	
	(1)*	(2)**	(1)*	(2)**	(1)*	(2)**	(1)*	(2)**	(1)*	(2)**
1.8	14.4	12.36	13.22	13.25	1.08	0.90	3.4	1.8	7.44	7.27
6.6†	15.6	12.86	12.5	13.34	1.25	0.96	4.1	1.2	7.26	7.39
1.8	26	12.6	11.86	13.0	2.36	0.97	6.8	1.9	7.3	7.33
5.9†	18.6	12.4	14.12	12.92	1.31	0.96	4.3	2.2	7.09	7.09
8	10.11	18.34	12.64	7.54	.80	1.06	4.5	1.6	—	—
6.5	11.16	10.46	7.18	6.14	1.55	1.75	4.4	2.3	7.28	7.25
4.2†	12.25	15.69	7.98	5.17	1.53	3.06	3.2	1.6	7.16	7.24
6.7	21.41	11.02	10.86	12.58	1.97	0.97	4.2	2.2	7.26	7.21
7.2	11.10	13.97	6.49	3.94	1.71	3.50	7.6	3.6	7.31	7.29

* Before injection of insulin.
** At lowest blood sugar level after insulin.
† Given in two doses separated by brief interval.

both the alterations in the blood pressure and the blood sugar. Phosphorus, however, showed a constant tendency to decrease during hypoglycemia. Such ionic changes are probably of no significance in connection with the phenomena studied. This is obvious with respect to the K/Ca ratio which varies in a random fashion. Although the blood phosphorus decreases regularly with decreasing blood sugar, the *rate* of decrease of these two substances is quite different, and the augmented blood pressure response to oxygen deficiency is greatest at the lowest blood sugar level, but not at the lowest phosphorus concentration.

As Table II shows, the changes in pH were insignificant except in the first two experiments in which the change was greater than 0.1. While in both experiments the blood pressure reaction increased with falling blood sugar, the pH increased somewhat in one case and decreased in the other. It is improbable therefore that changes in the acidity of the blood play an important part in the reactions just described.

III. Discussion

The uniformity of the results indicate that with progressive hypoglycemia the blood pressure response to low oxygen-nitrogen mixtures progressively increases. This effect is attributed solely to the changes in blood sugar level and to the duration of the hypoglycemic state. The first contention is proved by numerous experiments in which it was found that: (i) The increase in response corresponds to the blood sugar level and not to the amount of insulin injected. (ii) The increase in blood pressure response to low oxygen is largely independent of other chemical changes which may occur in the blood. (iii) The normal blood pressure response is restored by injection of glucose.

The second contention is based on the fact that the blood pressure response to 6.2 per cent oxygen increases when a given low blood sugar concentration is maintained for some time. With regard to the effect of the various sugars, it is interesting to state that the effectiveness follows the series: glucose > levulose > galactose, which is identical with that found by MacLeod and collaborators (1923, 1924) when they studied the curative effects of various sugars in insulin coma. It was noted that galactose improves respiration although it fails to lower the blood pressure response to the inhalation of oxygen deficient gas mixtures. Since it is unlikely that the excitability of two medullary centers such as the respiratory and the vasomotor center react differently to galactose the findings may indicate a different locus of action in the two cases.

Extensive studies by Gellhorn and Lambert (1938) have shown that the blood pressure response to low oxygen tensions is greatly modified by respiration. Experiments were, therefore, carried out to study the blood pressure reaction to 6.2 per cent oxygen at various blood sugar levels in dogs with pneumothorax and artificial respiration. Since the results were similar to those described in this paper the increased blood pressure response to 6.2 per cent oxygen cannot be attributed to alterations in respiration. Moreover, the differences observed are much greater than those which can be obtained by quantitative changes in respiratory volume.

The greatly increased blood pressure response to 6.2 per cent oxygen indicates that hypoglycemia reduces the rate of oxidations in the central nervous system to such an extent that a further reduction by the inhalation of 6.2 per cent oxygen produces a rise in blood pressure somewhat like that found when oxygen in very low concentrations is inhaled. Although this hypothesis has been supported by our investigations the mechanism by which this is achieved is still obscure. Lambert and Gellhorn (1938) have recently shown that the rise in blood pressure following the inhalation of low oxygen tensions is exclusively due to the stimulation of chemoreceptors in the carotid and aortic bodies, *i.e.*, elimination of their end organs by bilateral vagotomy and denervation of the carotid sinus areas, reverses the blood pressure reaction to low oxygen tension. A fall in blood pressure ensues whereas before the denervation, or after restoration of the temporaily blocked vagus fibers, a rise in blood pressure accompanies the inhalation of low oxygen tension. In

the light of these experiments it is probable that the responsiveness of the medullary centers to afferent impulses originating in the chemoreceptors (carotid body and the arch of the aorta) is increased by hypoglycemia. A final decision of these questions will be given in experiments in animals with removal of all "buffer" nerves.

Finally, attention must be called to the principal differences between the effects of pure oxygen deficiency and those produced by the combination of hypoglycemia and inhalation of low oxygen. The blood pressure response to inhalation of 6.2 per cent oxygen at low blood sugar level is much greater than can be obtained by inhalation of a gas containing a much smaller oxygen concentration or even by inhaling pure nitrogen. Several experiments were carried out in which narcotized dogs inhaled 6, 5, 4, 3, and 2 per cent oxygen, and also pure nitrogen for 1–3 minutes. It was found that those oxygen concentrations which could be inhaled for 3 minutes without causing respiratory and circulatory failure (*i.e.*, 3 per cent oxygen or higher) never caused a rise in blood pressure comparable to that obtained on inhalation of 6.2 per cent oxygen in hypoglycemia. If the oxygen concentration is too low (3 per cent or less) heart failure develops rapidly and the blood pressure falls.

This fundamental difference in the effects of hypoglycemia combined with the inhalation of a moderately reduced oxygen concentration, and of nitrogen inhalation at a normal blood sugar level, becomes understandable if we take into account the fact that hypoglycemia reduces the oxidation rate more in the central nervous system than in other organs of the body. The central nervous system consumes carbohydrates almost exclusively. Its respiratory quotient approaches unity (Lennox, 1931; Dickens and Simer, 1931; Himwich and Nahum, 1932). The heart, however, is able to do work with much lower respiratory quotients. The combination of hypoglycemia with inhalation of low oxygen gas mixtures seems to diminish the oxidative processes in the central nervous system more than any other known procedure without causing death by heart failures. The greatly increased blood pressure response may be taken as an indication of the tremendous excitation of the sympathetic centers. The significance of these findings for the schizophrenia problem is discussed elsewhere (Gellhorn, 1938).

IV. Summary

The relation between hypoglycemia and anoxia, as far as the central nervous system is concerned, has been tested by investigating the blood pressure reaction in dogs to a given degree of anoxia obtained by inhalation of 6.2 per cent oxygen. It is known that increasing degrees of anoxia produce proportionately greater rises in blood pressure. On this basis the blood pressure reaction to a given oxygen concentration (6.2 per cent) may be used as an indicator of the degree of oxygen want in the central nervous system. The experiments have shown:

1. Insulin, by virtue of the hypoglycemia produced, causes augmentation in the blood pressure rise to a given degree of oxygen deficiency.

2. This effect is a function of the decrease in the level of blood sugar. This is indicated by: (a) The failure of this augmentation effect to appear in those experiments where insulin did not significantly alter the blood sugar level. (b) The observation that the blood pressure response to the inhalation of 6.2 per cent oxygen varied inversely as the blood sugar concentration. (c) The fact that the restoration of the blood sugar level after hypoglycemia, by the intravenous injection of glucose, diminishes the blood pressure response and restores it to normality.

3. Of the other monosaccharides: fructose, although to a lesser degree than glucose, is capable of lessening the degree of blood pressure response to oxygen deficiency; galactose fails to bring about such reversal.

4. The ionic changes in the blood (K, Ca, H) appear to bear no relation to the phenomenon. The K/Ca quotient shows random variations. The phosphorus concentration decreases with falling blood sugar. The rate of change is, however, different for phosphorus and for blood sugar. The blood pressure response is dependent on the change in blood sugar rather than the change in blood phosphorus.

5. That the oxidative processes in the brain are diminished in hypoglycemia is further indicated by the fact that inhalation of 6.2 per cent oxygen may induce Cheyne-Stokes breathing when the blood sugar is low, although it fails to do so when the blood sugar level is restored by injection of glucose, levulose, or galactose.

6. The increased blood pressure response to oxygen deficient gas mixtures (6.2 per cent oxygen) observed in hypoglycemia is greater than the blood pressure rise obtained on inhalation of pure nitrogen at normal blood sugar levels. This is due to the fact that hypoglycemia, in contrast with the effects of nitrogen inhalation, reduces the rate of oxidation in the brain more than in other tissues. Therefore, a greater reduction in the oxidative metabolism can be achieved and maintained in the brain by combination of the hypoglycemic state with the inhalation of 6 per cent oxygen than by inhalation of nitrogen. In the latter case heart failure develops rapidly and the blood pressure falls.

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THE DISTRIBUTION OF THE ALPHA RHYTHM OVER THE CEREBRAL CORTEX OF NORMAL MAN*

MORTON A. RUBIN

From the Biological Laboratories, Clark University, and the Research Service of the Worcester State Hospital, Worcester, Mass.

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THE MOST characteristic spontaneous electrical activity of the human cerebral cortex is a 10 per sec. oscillation (α rhythm), yet its origin and distribution over the cortex is still undecided. Adrian and Matthews[1] and Adrian and Yamagiwa[2] reported evidence for the origin of the α rhythm in the occipital lobes. This view was supported by observations of Tönnies.[20] On the other hand, Berger[6,7,8] maintained that α rhythm could arise in parts of the cortex other than the occipital lobes. In agreement with Berger, Foerster and Altenburger[11] found a well defined 10 per sec. rhythm over many regions of the cortex, and Jasper and Andrews[14] concluded that the precentral α rhythm is independent of the occipital lobes for its origin.

Preliminary experiments revealed that the two opposing interpretations could be substantiated *depending on the method of recording* employed. The present investigation is primarily concerned with (a) the determination of which method of recording electro-encephalograms from electrodes on the scalp gives the truer representation of the α activity of the brain tissue under the electrodes, and (b) the bilateral distribution of the α rhythm over the cerebral cortex.

APPARATUS AND PROCEDURE

Two independent, well-matched amplifiers and ink-writing undulators built by Mr. A. M. Grass were used in conjunction with two filter systems tuned to 10 cycles per sec. The amplification was kept constant throughout the experiments, a 5 mm. pen excursion corresponding to 50 microvolts.

The electrodes were flattened pellets of lead solder, about 2 mm. in diameter, fixed to the scalp with collodion. Electrical contact was made with Sanborn electrode paste. We shall use the term "monopolar" to indicate recording between one lead over active cortical tissue and an earthed (reference) lead on some indifferent tissue (*i.e.*, the mastoid processes). The term "bipolar" will indicate potential changes between two active leads over cortical tissue which are recorded with balanced (push-pull) input amplifiers.

The subject, with his eyes closed, reclined on a bed in a semi-darkened, quiet, shielded room. In the majority of the experiments, performed on 17 adult males, the electrodes were arranged in two rows from the back to the front of the head over both cerebral hemispheres about 3 cm. to either side of the midline. Usually 7 electrodes were fixed to the scalp on each side and potentials from the corresponding leads on both sides were recorded simultaneously. Records were obtained from each subject on at least two different days, sometimes being repeated one or more times on the same day. Fig. 1 illustrates the customary placement of active leads along the head. The electrodes were always placed roughly over the same regions of the cortex by the use of Krönecker's method of cranio-cerebral topography so that differences in size of individual heads were corrected for (Fig. 1).

At least 3 consecutive α waves with amplitudes of 7 microvolts or more were arbitrarily required to constitute an α rhythm. (This criterion was first suggested by Dr. Hallowell Davis and Pauline A. Davis in a personal communication.) The percentage of

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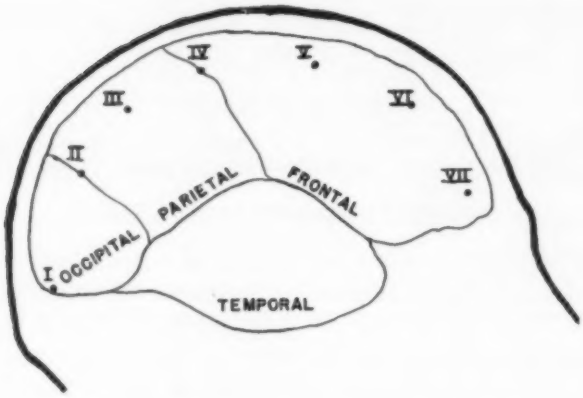

FIG. 1. Diagrammatic representation of one hemisphere of the cerebral cortex illustrating the placement of active leads over it. Roughly, electrode I is over the posterior tip of the occipital lobe; II, over the occipito-parietal fissure; III, mid-parietal; IV, central fissure (fissure of Rolando); V, VI, and VII divide the frontal lobe into 3 approximately equal parts. Usually an equal number of electrodes were similarly placed over the other hemisphere. The distances between successive electrodes were not exactly equal, but about 5 cm. apart for most individuals.

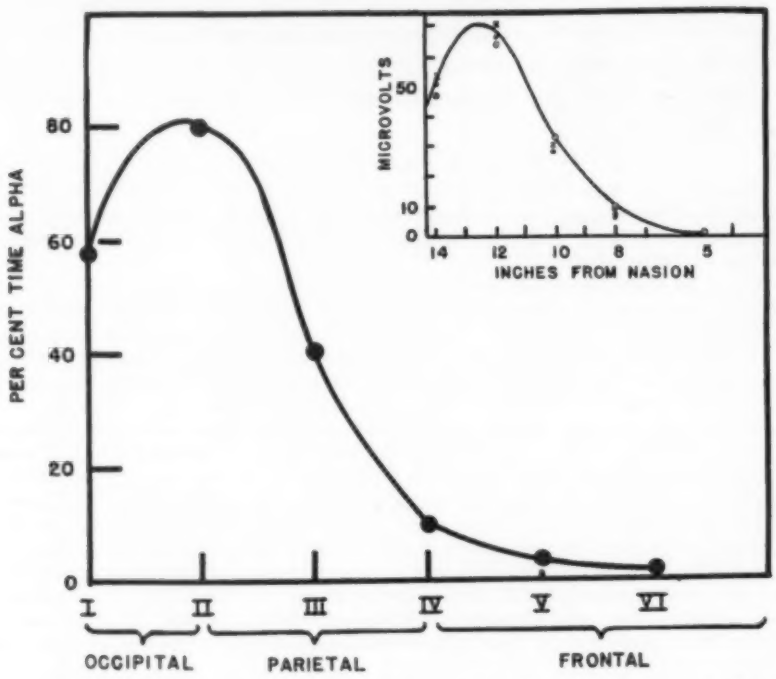

FIG. 2. Distribution of *per cent time alpha* over the right cerebral hemisphere of J. D. (Bipolar Recording). Note the similarity of this curve to the one in the insert (from Adrian and Yamagiwa, *Brain*, 1935, *58:* p. 339, Fig. 21B). The distance between the electrodes is almost the same in both curves.

2 consecutive meters of record occupied by the α rhythm (*per cent time alpha*) was used as the measure of the amount of α activity in the various cortical areas. (The speed of the moving paper tape was 30 mm./sec. Therefore, it took slightly more than a minute to obtain 2 meters of record.)

Results

When electro-encephalograms were recorded between successive pairs of active leads (bipolar) separated by about 5 cm., the *per cent time alpha* was distributed over the cortex* in a manner similar to that found by Adrian and Yamagiwa[2] for the average amplitude of the α waves (Fig. 2). The close

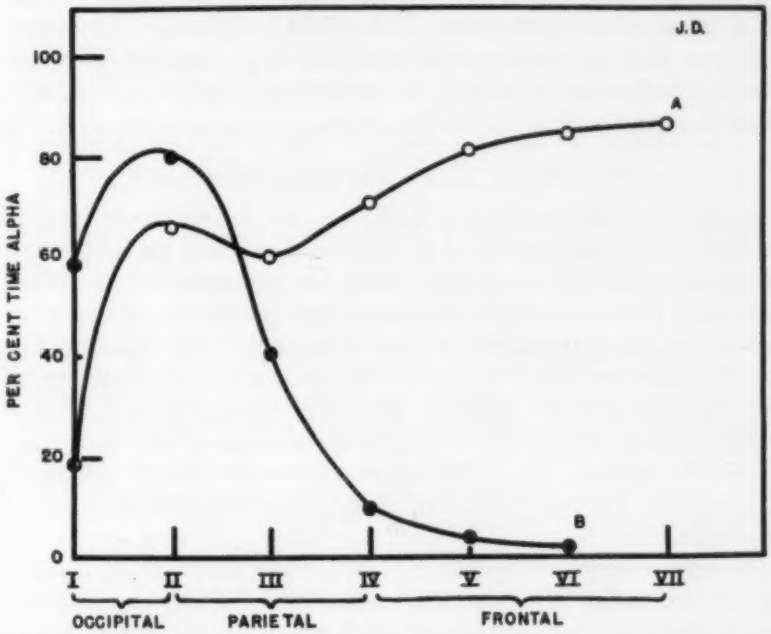

FIG. 3. Distribution of *per cent time alpha* over the right cerebral hemisphere in J. D. with monopolar recording (Curve A, open circles) and with bipolar recording (Curve B, solid circles). The data for the two curves were taken simultaneously and therefore are strictly comparable.

similarity between the two curves bears out the direct relationship often observed between the *per cent time alpha* and the amplitude of the α waves making up the rhythm. Furthermore, Fig. 2 illustrates the ease with which Adrian and Yamagiwa's results may be reproduced, and is in harmony with an occipital origin of the α rhythm. They also used bipolar recording in their experiments. However, when records were obtained from the same electrodes and the same subject as in Fig. 2 using monopolar instead of bipolar leads,

* We cannot insist on the precise shape of the individual parts of the curve in Fig. 2 or in any of the other figures in this paper, since the points on the curves are about 5 cm. apart. We can say, however, that it is legitimate to draw smooth curves between the points since our results from closely spaced (1 cm. apart) electrodes indicate that the points of inflection are not sudden or very sharp.

the *per cent time alpha* was found to be distributed in a different way. The curve (A) connecting the open circles in Fig. 3 represents the distribution of *per cent time alpha* with monopolar recording. The solid circles curve (B) is the same as that in Fig. 2.

The two curves are much alike for the occipital and the first part of the parietal areas (Fig. 3). The *per cent time alpha* distribution over the frontal cortex, however, differs markedly with the two methods of recording. Curve A supports the generalized origin of the α rhythm, claimed by Berger, since a higher *per cent time alpha* in the frontal lobe could not possibly be due merely to spread of the rhythm from the occipital lobe. The amplitude of the α waves throughout most of the frontal lobe was appreciably greater than in the occiput. The type of distribution curve obtained must depend on which of the two recording techniques is employed. Accordingly, a series of control experiments was devised to obtain a better understanding of these methods.

Monopolar (Grid-Ground) Recording

(1) *Is the grounded (reference) lead truly an "indifferent" lead?* The *per cent time alpha* from any region of the cortex was the same whether the mastoid processes or the ear lobes were used for reference points. When active electrodes were placed on each of the mastoid processes, the ears serving as reference tissue, no appreciable *per cent time alpha* was observed. The same was true when the earthed lead was placed on the bridge of the nose. Bipolar recording between the two mastoid processes gave essentially the same results, which were independent of the absolute value of the occipital *per cent time alpha*. We believe, therefore, that electrodes placed on the mastoid processes, on the ear lobes, or on the bridge of the nose constitute satisfactory reference leads.

(2) *Distance between electrodes.* Records were taken from the same grid electrode on the scalp, using the nose and mastoid electrodes simultaneously as reference leads. The *per cent time alpha* from the various electrode positions along the head was always the same for both reference and given active electrode combinations (in fact, the two records were superimposable), although the distance from nose to the active electrode and from mastoids to the same active lead was never equal.

We conclude that with monopolar recording the *per cent time alpha* obtained is a measure of the amount of activity under the active electrode, and that neither the reference lead nor the distance between it and the active electrode contributes materially to the picture.

Bipolar (Push-Pull) Recording

The distance between active leads in bipolar recording undoubtedly plays a rôle in determining the "net" potential changes recorded between the leads. It is, however, by no means the most important factor. The different *per cent time alphas* (see Fig. 3, A and B) obtained with the monopolar and bipolar methods may result from factors operating singly or, more probably, in un-

predictable combinations in the latter method. From the magnitude of the *per cent time alpha*, phase relations, synchronization of α "bursts" of activity and "silent" periods, and amplitude of the α waves occurring under both electrodes simultaneously determine to what degree the true α activity which exists under each electrode may be distorted by bipolar recording. The way in which these variables may act is illustrated by the following experiment.

Five electrodes were placed at intervals of 1 cm. between our standard electrodes II and III (occipito-parietal fissure to mid-parietal region). This region was chosen since approximately the same distribution curve is obtained here with both monopolar and bipolar recording, and because marked phase shifts occur in this region (Adrian and Yamagiwa[2]). Records were obtained from the various bipolar combinations simultaneously with monopolar arrangement of the same active electrodes, so that the *per cent time alphas* in

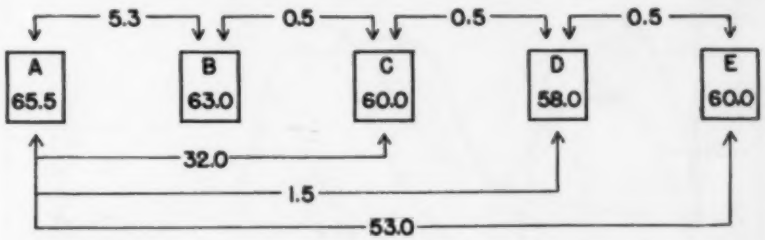

FIG. 4. Electrodes A, B, C, D, and E placed at intervals of about 1 cm. between the occipito-parietal fissure to the mid-parietal region. Lead A corresponds to our standard lead II (occipito-parietal fissure) and electrode E to standard lead III (mid-parietal). Figures within the squares represent the monopolar *per cent time alpha* for each electrode placement. All other figures represent *per cent time alphas* obtained from combinations of the same electrodes using bipolar recording. Subject J. D. Compare these monopolar values with those between leads II and III in Fig. 3.

Fig. 4 are comparable. Bipolar leads give markedly different *per cent time alphas* from monopolar leads, and they do not bear any constant relationship to the latter. The monopolar *per cent time alphas* for electrodes A, D, and E were about the same, namely, approximately 60.0. Bipolar *per cent time alpha* between A and D, however, was 1.5, and that for A to E 53.0. Recording between bipolar leads spaced farther and farther apart along the head (I–II, I–III, I–V, etc.) and between analogous leads on each hemisphere (II left—II right) gave similar anomalous results. Obviously, we are not dealing simply with an algebraic difference between the amounts of α activity under the two electrodes.

We have obtained bipolar *per cent time alphas* which were much higher than that under each electrode alone. In such cases, even when the grid-ground *per cent time alphas* under each electrode were identical, the bursts of α activity did not occur simultaneously under both electrodes, but, in the main, first under one and then under the other. The net effect of this situation was an almost continuous α rhythm for certain stretches of record and much less activity in other portions of the record where more synchrony of α bursts

occurred under the electrodes. On the other hand, even when the bursts of activity occur simultaneously under both electrodes, the amplitude of the α waves in the bipolar tracing may be considerably lower than in either of the monopolar tracings. Further complications in bipolar recording would also arise when the individual α waves under both electrodes are not in phase.

The Bilateral Distribution of Per Cent Time Alpha

(1) *Foci of maxima.* It was unusual for both hemispheres to show the same distribution of *per cent time alpha.* A typical set of curves is shown in Fig. 5. There usually was at least one other region of maximal α activity be-

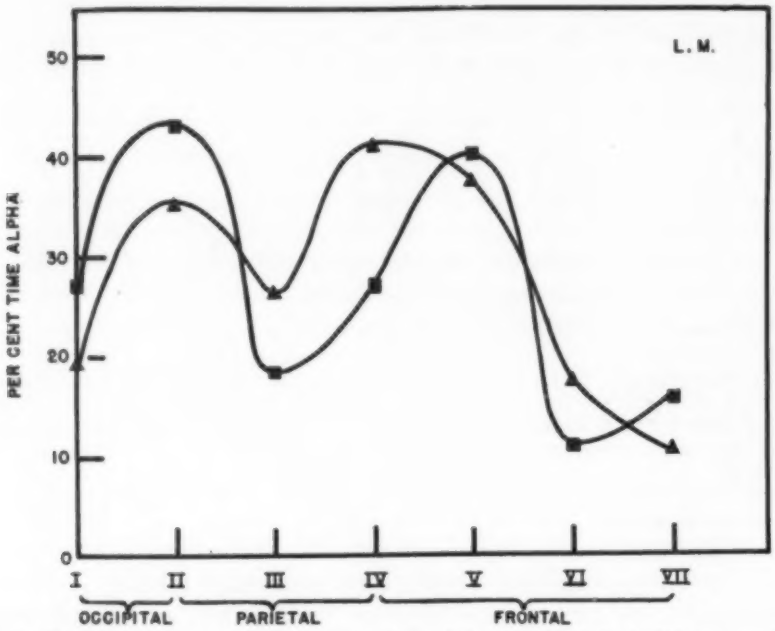

Fig. 5. Distribution curves of *per cent time alpha* for the left (solid squares) and the right (solid triangles) cerebral hemispheres of L. M. with monopolar recording, illustrating differences in magnitude and foci of maxima of *per cent time alpha* in the two hemispheres.

sides the occipital lobes. This other region was not always in the same portion of the frontal lobe in each hemisphere. For example, in Fig. 5 the left frontal lobe maximum was under lead V, whereas on the right side it was under electrode IV.* The curves from leads I to III, however, were usually the same for both hemispheres, differing only in absolute values.

(2) *Variability.* The frontal distribution curves varied a great deal from individual to individual (compare Figs. 3A and 5). For a given subject it may vary within comparatively short periods of time or from day to day. These statements apply to the majority of the 17 subjects studied, although we

* The distance from IV to V (about 5.0 cm.) is too great to explain the difference in foci of maxima in the frontal lobes on the basis of an anatomical asymmetry of the two hemispheres.

have seen some individuals whose distribution of *per cent time alpha* was relatively constant. Fig. 6 illustrates the fluctuation of the distribution curves of subject O.S. for the right cerebral hemisphere only. Curve B was obtained from the same electrodes as Curve A, but one half-hour later. Curve C was obtained from the same individual one day later.

The first portions of all 3 curves are quite similar. Although the magnitude of *per cent time alpha* may vary within the limits of variability for a

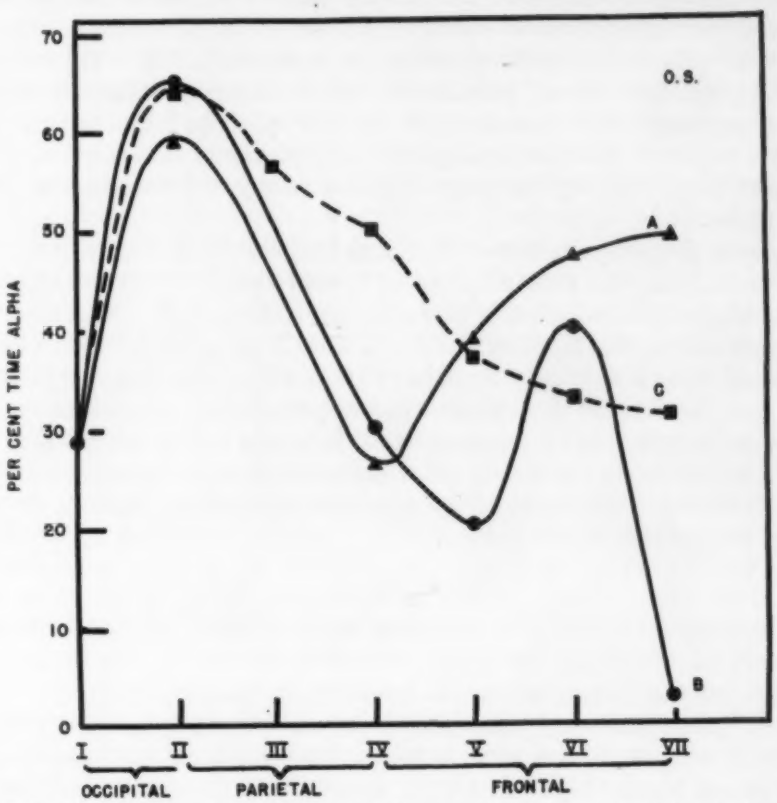

FIG. 6. The distribution of *per cent time alpha* over the right cerebral hemisphere of O. S. obtained with monopolar leads. B, taken ½ hour after A; C, one day later.

given individual, the shape of the distribution curve for leads I–IV is extremely constant. In general, this portion of the curve is the same from person to person irrespective of absolute *per cent time alpha* values.

The extreme variability of the frontal *per cent time alpha* may be the source of another complication in bipolar recording, since the relationship between successive pairs of electrodes changes so radically and frequently. For example, one subject who had a very low occipital *per cent time alpha* showed almost no α activity over the left frontal lobe on one day. On another day much more α activity was found under lead VII than under lead II.

(3) *Synchrony of bursts of α activity in the two hemispheres.* The bursts of

α waves from the two cerebral hemispheres seldom occurred simultaneously in the occipital lobes,* especially in individuals with low or medium *per cent time alphas*. As one progressed anteriorly along the head, synchronization of the bursts of α activity from the two hemispheres became much greater in most cases, until finally almost perfect unison was present in the anterior portion of the frontal lobes. However, this was not true for all the subjects, especially those with very high *per cent time alphas*. Berger[6,8] had previously reported somewhat similar differences between the two hemispheres and considered them as evidence in favor of the view that regions other than the occipital lobes could produce the α rhythm. Furthermore, bursts of α activity and the "silent" periods between them were seldom synchronized in the various regions of a hemisphere. In view of these facts, one may infer that the α rhythms in both hemispheres are relatively independent of each other,† and that the α rhythm may originate in any of the various regions of a hemisphere.

(4) *Alpha frequency*. It was often found that the frequency of the α waves in the frontal lobes was slower by one or two cycles than that in the occiput. The objection might be raised that we are not dealing with the same rhythm in the back and in the front of the head. This frequency difference was not found in all individuals, and regardless of whether the frequency was the same or not, the frontal rhythm was just as completely obliterated on opening the eyes as was that of the occiput. This would argue against any specificity of the α rhythm for visual functioning. The α rhythm seems to be an electrical activity common to all parts of the cerebral cortex, and it can be produced everywhere in the cortex.

Discussion

It is apparent that bipolar recording is not satisfactory for determining the amount of α activity from the cerebral cortex. Only the occipital and part of the parietal lobes give similar results with both methods of recording. "Standard" placements of bipolar electrodes over various regions of the frontal cortex, therefore, do not seem feasible. We consider monopolar recording superior to the bipolar method only for determining the amount of α activity (*per cent time alpha*), recognizing that bipolar recording may offer special advantages when employed for investigating other aspects of the electroencephalogram.

The evidence of Adrian and Yamagiwa[2] on phase change studies along the head favored the occipital origin of the α rhythm. Jasper and Andrews[14]

* Liber[17] has reported ependymal streaks and accessory cavities in the tip of one or both occipital horns (most frequently in the right hemisphere) in 16 out of 50 unselected human brains. He attributed the pathology to occlusion of the occipital horn by the growth of tissues surrounding it. This might be at least partially responsible for the differences in electrical activity which we have observed in the two occipital lobes of many subjects.

† Jasper and Andrews[13] found no constant phase relationship between the α activities under electrodes over the left and right occipital lobes. They regarded this as evidence of a certain amount of independence of activity between the two occipital fields.

have confirmed their observations in some subjects, but in other subjects the phase changes along the head were not in agreement with Adrian and Yamagiwa's interpretation. We have not studied the temporal α rhythm, but Laugier and Liberson[16] report that the origin of the temporal rhythm is not the same as that for the occipital rhythm.

The α rhythm may originate in the occipital cortex and then may be conducted to other regions of the cortex by sub-cortical pathways. If this were true, we should expect to find rather close synchronization between the bursts of α activity in the occipital lobes and other cortical areas. Actually, this is not the case. Moreover, preliminary investigations (in collaboration with Drs. Hoagland, Cameron, and Tegelberg) on the relationship between hypothalamic and cortical potentials in man show that (a) an α rhythm is never present in the hypothalamus unless it occurs also in the cortex, and that (b) the *per cent time alpha* is higher in the cortex than in the hypothalamus. This evidence is in favor of the generalized origin of the rhythm over the cortex, and it indicates that the rhythm arises spontaneously from cortical cells independent of other central nervous influence.

We have recently completed a study of the variability of the occipital *per cent time alpha* (Rubin[19]). The variability of the *per cent time alpha* in most of the other cortical areas seems to be appreciably greater than that in the occipital lobes although we have not systematically investigated the former. Judging from the occipital variability, the instability of the frontal *per cent time alpha* is not accountable for in terms of any variability inherent in the processes producing the α rhythm, but is rather the result of other nervous influences playing upon it.

The greater part of the cerebral cortex receives afferent fibers from the thalamus (Ariëns Kappers, Huber, and Crosby[3]). Since, under our conditions of recording, the subject's eyes are closed, we would not expect the occipital α rhythm to be affected by afferent impulses relayed to the occipital lobes by the thalamus. In fact, the occipital α rhythm is just as unstable as the frontal rhythm if the eyes are kept open while electro-encephalograms are being taken. The frontal lobes, however, may be influenced by thalamocortical impulses set up by changes in the subject's external and internal environment. The frontal lobes also receive connections from the hypothalamus (Papez[18]). In view of Bard's[4] evidence that the hypothalamus elaborates afferent impulses that reach it, giving them "emotional" content, even slight, transitory "emotional" excitation might well be reflected in the frontal cortex. Recently Grinker[12] has reported that electrical stimulation of the hypothalamus in the cat and in man altered both the autogenous electrical activity of the hypothalamus and that of the cortex. Grinker's observations and the well-known fact that apprehension, embarrassment, etc., usually inhibit the cortical α rhythm are consistent with the notion that sub-cortical brain levels contribute to the marked fluctuations of the frontal lobe *per cent time alpha*.

The amount of α activity in the cortex may not be simply a direct result of the activity of lower brain levels. Bartley[5] has shown that the entire cortex

of the dog is involved to varying degrees in response to sensory stimuli; the greatest response occurs in only one or two areas, but other areas are also affected. Blake and Gerard,[9] from their experiments on sleep, have suggested that indirect channels from one cortical region may influence other regions, and that the pre-existing state of the cortical neurons determines their response at any given time. Not only do intracortical pathways probably exist within a hemisphere, but pathways from one hemisphere to the other also have been reported. For example, evidence presented by Kornmüller[15] and by Elsberg and Spotnitz[10] indicates the presence of a crossed pathway which connects one frontal lobe with the occipital lobe of the opposite side.

Summary and Conclusions

Electro-encephalograms were obtained from 17 subjects to determine the distribution of the α rhythm over the cerebral cortex and to evaluate the use of monopolar and bipolar recording for this purpose. The following results were obtained:

1. Monopolar recording from electrodes on the scalp gives a truer representation of the amount of 10 per sec. activity (*per cent time alpha*) in the cerebral cortex than does bipolar recording.

2. There were at least two regions of the cortex which showed maxima of α activity—usually some part of the occipital and frontal lobes. The curve describing the occipital lobe distribution of *per cent time alpha* was very stable and could be reproduced, even over long periods of time. The distribution curve for the frontal lobe, however, was extremely variable, fluctuating over short intervals ($\frac{1}{2}$ hour) and from day to day.

3. The bursts of α waves from the two cerebral hemispheres of some individuals were least synchronized in the back of the head, more perfect unison between the two rhythms being obtained the further anterior one recorded along the head.

4. The bursts of α activity and the "silent" periods between them in the occiput did not occur simultaneously with the bursts and "silent" periods in the frontal lobes. Often the frequency of the α waves in the frontal lobes was found to be slower than that in the occipital lobes; waves of both frequencies, however, were obliterated when the subject opened his eyes.

5. The evidence reported here indicates that the α rhythms of the two hemispheres are relatively independent of each other, and that the α rhythm may arise in all regions of the cerebral cortex.

6. Factors which might account for the marked fluctuation of the frontal lobe *per cent time alpha* are discussed.

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EFFECTS OF BLOOD PRESSURE CHANGES ON CORTICAL POTENTIALS DURING ANESTHESIA

H. K. BEECHER, F. K. McDONOUGH, AND A. FORBES
From the Department of Physiology of the Harvard Medical School and the Surgical Laboratory of the Massachusetts General Hospital, Boston

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DURING a study of the effects of anesthetic agents upon the electrical activity of the cerebral cortex it appeared that some of the outstanding differences between the agents might be due to their secondary actions. For example, it has been shown[5] that the pattern of cortical action potentials in cats under ether varies widely from that found when pentobarbital is the anesthetic agent. Deep anesthesia under the latter drug is frequently associated with a low systemic blood pressure. Any attempt to evaluate the differences between such agents requires a consideration of the influence of low blood pressure *per se*. The purpose of this paper is to describe the rather striking cortical effects induced by altering the level of the systemic arterial pressure.

APPARATUS AND METHOD

Animals. Cats were studied under third stage (surgical) anesthesia. The right posterior sigmoid gyrus of the cortex was exposed. Activity was recorded from the region of the sensory area.

Anesthetic agents. Ether and pentobarbital sodium were used. Ether was administered through a tracheal cannula. When a high concentration was desired, all the air breathed was drawn over an ether surface. When a lighter degree of anesthesia was indicated, a by-pass for air was opened. Pentobarbital sodium was administered intraperitoneally, using 0.33 mgm. per kgm. Deep anesthesia was obtained by increasing the dose by 50 to 100 per cent. The effects of changes in the blood pressure were studied only when the level of anesthesia had become constant as determined by identical flexion reflexes following sciatic stimulation.

Blood pressure and its regulation. The blood pressure was recorded from a glass cannula inserted into the left common carotid artery. The cannula was filled with 5 per cent citrate solution. The blood pressure was regulated in the manner described by Cannon,[4] *i.e.*, through cardiac tamponade. A cannula is tied into the pericardium and Ringer's solution introduced into the pericardial sac; the Ringer's solution flows from a levelling bulb and the intrapericardial pressure is regulated as desired.* The systemic arterial pressure can thus be abruptly altered and held at any level below the normal, or returned quickly to normal. This method greatly increases the intracranial venous pressure. Lowering of the blood pressure by bleeding (see below) caused a comparable effect on cortical activity. It seems unlikely that the high venous pressure of itself produced any effect. When the blood pressure was lowered by bleeding (one case) it was not possible to restore the pressure quickly to normal. This technic was accordingly not suitable for the experiment.

Sensory stimulation. The central end of the *left* sciatic nerve was inserted into tube electrodes which were placed in circuit with stimulating apparatus consisting of a hand

* It is customary to use a glass cannula for this procedure. We found, however, that one prepared in the following way was easier to insert. Remove the bevel from the end of an ordinary 18 gauge needle, and then place a drop of solder around the orifice, making a terminal knob. Place another drop of solder 2 mm. above this on the shaft of the needle. Hold the pericardium up with two pairs of blunt forceps; prick a hole in it with a needle and then force the cannula into the sac until both knobs are inside. Tie above each of these, and allow the pericardium to fall back into its natural position. During the time the chest is open oxygenation must be maintained by positive pressure respiration.

operated mercury contact key, a 1.5 volt dry cell, a string galvanometer signal device (Forbes and Cattell[6]), and a Harvard inductorium. The stimuli were make and break shocks spaced from one to three seconds apart, usually followed by a rapid series of shocks (by hand). The homolateral nerves to the hamstring muscles were left intact in order that a flexion response of the lower leg might occur and be recorded on a smoked drum. The activity of this reflex following stimulation was used as one indication of the depth of anesthesia.[5]

Electrodes. Various types of electrode were used: first, plates with one plate on the cortex and the other outside the skull; second, "bipolar" surface electrodes having a separation of 1.5 mm. were employed; finally, we used concentric electrodes. These with their

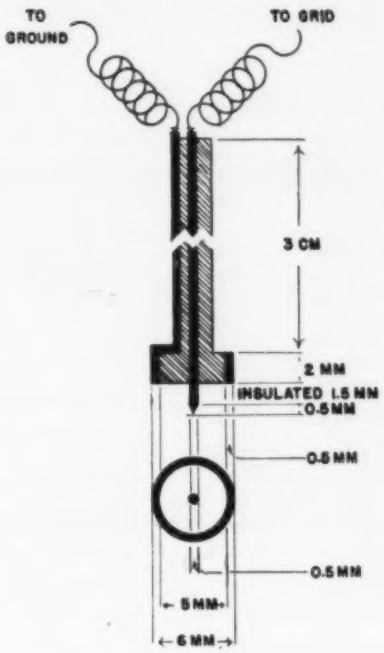

FIG. 1. The concentric electrodes; section and end view.

dimensions and general arrangement are shown diagrammatically in Fig. 1. Potential differences were recorded between the surface of the cortex and the interior. The central electrode which was chosen as the grid lead, was formed as a spike and everywhere insulated except at its tip. The central spike was surrounded by a circular band, the ground lead. The electrodes were of silver supported by a hard rubber base. Fresh silver chloride was deposited upon them electrolytically each time before using.

The pictures obtained with the concentric electrodes do not differ fundamentally from those obtained with the other types. Recording with the concentric electrodes was more satisfactory since pulsation of the cortex from the heart beat and respiration is often troublesome with the bipolar electrodes. With the concentric electrodes disturbance from this cause is minimal, for the flange of the ground lead usually fills the opening in the skull made to identify the desired cortical position. The potential difference appears to be somewhat greater when the leads are taken from below the surface of the cortex and the surface rather than from two surface areas. This makes for a clearer recording of changes. The brain varies rather widely in volume at various levels of anesthesia, evidently as a result

of circulatory changes, and this usually necessitates adjustment of most electrodes. The concentric type described here requires less attention than the others. This type is also strong and durable.

Amplifier. The potential changes between the ground and grid leads were amplified by the direct-coupled apparatus described by Forbes and Grass[7] and recorded on film with a Hindle string galvanometer. A timer with 10 msec. units recorded on one margin of the film; a string and magnet were used for recording make, break and series (by hand) stimuli on the opposite margin.

Results

Notwithstanding wide variations in the "normal" pattern of electrical activity in the cortex, certain constant changes in this activity, such as de-

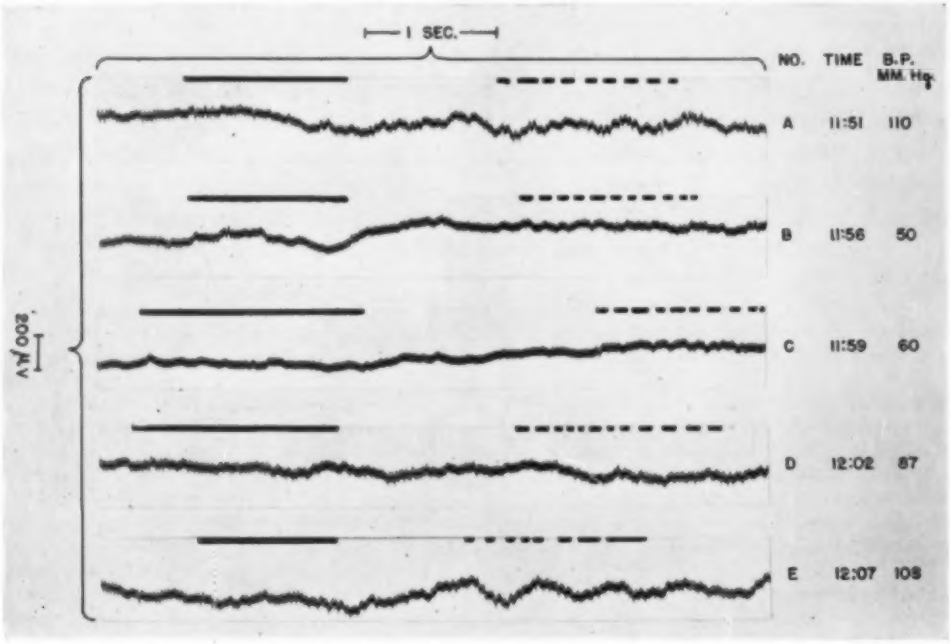

FIG. 2. This shows the effects of low blood pressure upon the cortical potentials under ether anesthesia. Reading from left to right a "make" shock is indicated by the beginning of the broad black band, a "break" by its termination. In this and all subsequent records an upward deflection signifies negativity of the grid electrode; this was always the central electrode which penetrated the cortex.

crease in potential of the waves, are correlated with depression of blood pressure. Other effects, such as the "spike" response,[5] more appropriately designated the secondary discharge (See Fig. 5C) can be elicited at one time but not at another. Probably this effect can be brought out only in a relatively narrow zone. It will be considered in the Discussion.

Ether

The dominant frequency of the rapid waves under ether is of the order of 40 per sec. (See Fig. 2). The basic frequency is not significantly altered by variations in blood pressure of the extent shown here. Prolonged depression

of the blood pressure will abolish the waves (See Fig. 3). When the concentric electrodes are used and the potential difference between the interior (2 mm. deep) and the surface of the cortex recorded, the largest of the rapid waves show an amplitude of about 60 micro-volts at a normal blood pressure. At a "shock" level (Fig. 2C), this amplitude is reduced by nearly 50 per cent.

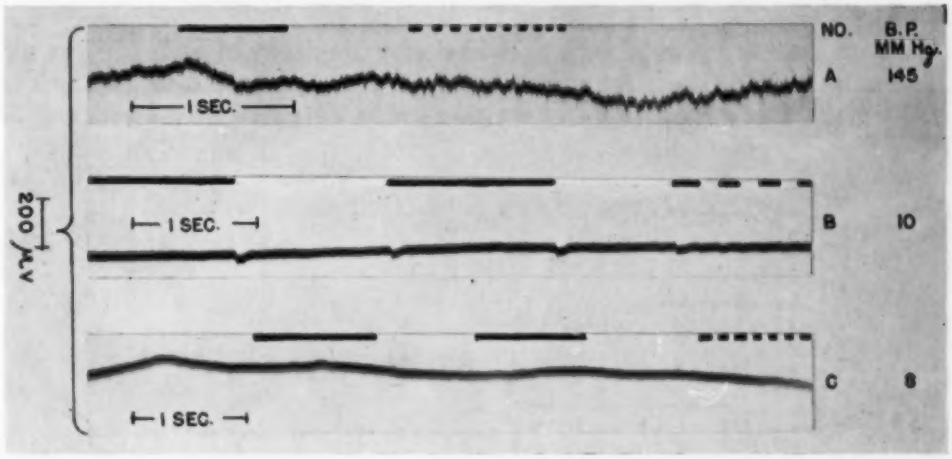

FIG. 3. Ether anesthesia. Blood pressure lowered by hemorrhage. This shows the appearance of the "secondary discharge" following sciatic stimulation, and its disappearance on repeated stimulation.

A true secondary discharge following sciatic stimulation was elicited under ether only when the animal was in poor general condition, following lowering of the blood pressure by hemorrhage (Fig. 3B). The disappearance of the effect following repeated stimuli is characteristic and evident here. This phenomenon occurs with a latency of 40 to 60 msec. It is clearly distinguished

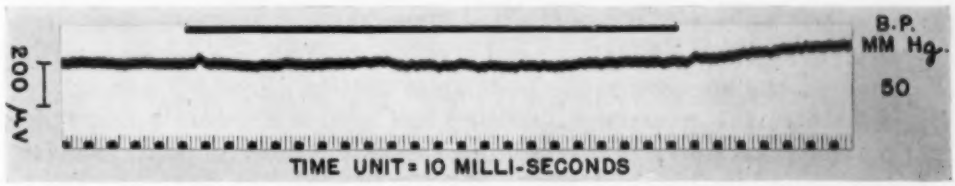

FIG. 4. A record of the arrival in the cerebrum of the afferent volley following sciatic stimulation. Ether anesthesia. Cortical activity depressed by low blood pressure.

from the arrival in the cerebrum of the afferent volley initiated by sciatic stimulation, both by its greater latency and by its absence in the response to all but the first one or two of a rapid series of stimuli.[5] The usual ether pattern is such that the arrival of this volley in the cerebrum cannot be detected; but, when the amplitude of the waves has been greatly depressed by a low blood pressure, the contrast is great enough to demonstrate it as in Fig. 4 (rapid

film). Restoration of the blood pressure to normal is quickly followed by a resumption of activity in the cortex (Fig. 2E).

Pentobarbital sodium

The pattern of activity under light anesthesia with this agent is somewhat similar to that found in unanesthetized cats.[5] The large excursions at normal blood pressure are of the order of 10 per sec. (Fig. 5). Superimposed upon these are smaller, more rapid waves having a frequency of about 25 per sec. The amplitude of the large excursions indicates a potential of as much as 200 microvolts, while the faster waves show a potential of the order of 50

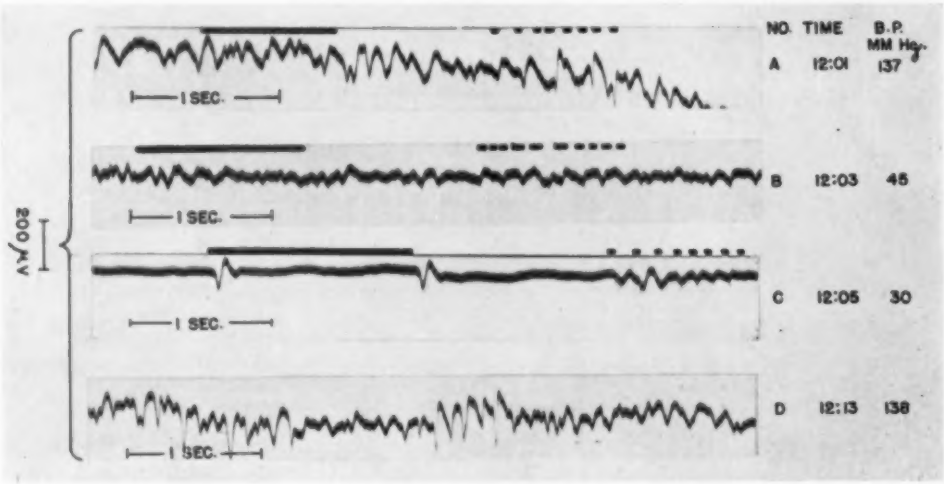

FIG. 5. This shows the various effects on cortical activity of several levels of blood pressure under light pentobarbital anesthesia. The "secondary discharge" has been evoked following sciatic stimulation and is recorded in record C. Its disappearance on repeated stimulation is also shown.

microvolts. Depression of the blood pressure can obliterate all spontaneous waves as in Fig. 6C and D. Restoration of a normal blood pressure is quickly followed by the appearance of the original pattern (Figs. 5D and 6E).

Heretofore the secondary discharge had been elicited only under deep pentobarbital anesthesia, under tribromethanol anesthesia or under asphyxia.[5] We have found in this study even when the anesthesia is light, as indicated by a very active flexion reflex, that it is easy to bring it out merely by lowering the blood pressure and stimulating the sciatic (Fig. 5C). The typical fatigue of the effect following rapid stimuli is also shown here. It appears possible to lower the blood pressure to such an extent that it becomes impossible to elicit the phenomenon, as in Fig. 6D. At the extreme left of this record a suggestion of the effect appears; in the later part it is absent.

DISCUSSION

Critical reduction of the systemic arterial blood pressure introduces numerous factors for consideration which have not yet been well evaluated in

their cortical effects. Undoubtedly important are the resultant anoxia and the fall in pH of the tissues. A clear understanding of these factors will require much further study. If, at a constant level of anesthesia the blood pressure is suddenly lowered, the flexion reflex produced by stimulation of the sciatic is abruptly depressed, the spontaneous activity in the cerebral cortex is diminished. Further lowering of the blood pressure results in failure of the flexion reflex, and if the pressure is lowered still further the recorded activity n the cortex disappears. These effects are identical with those induced by

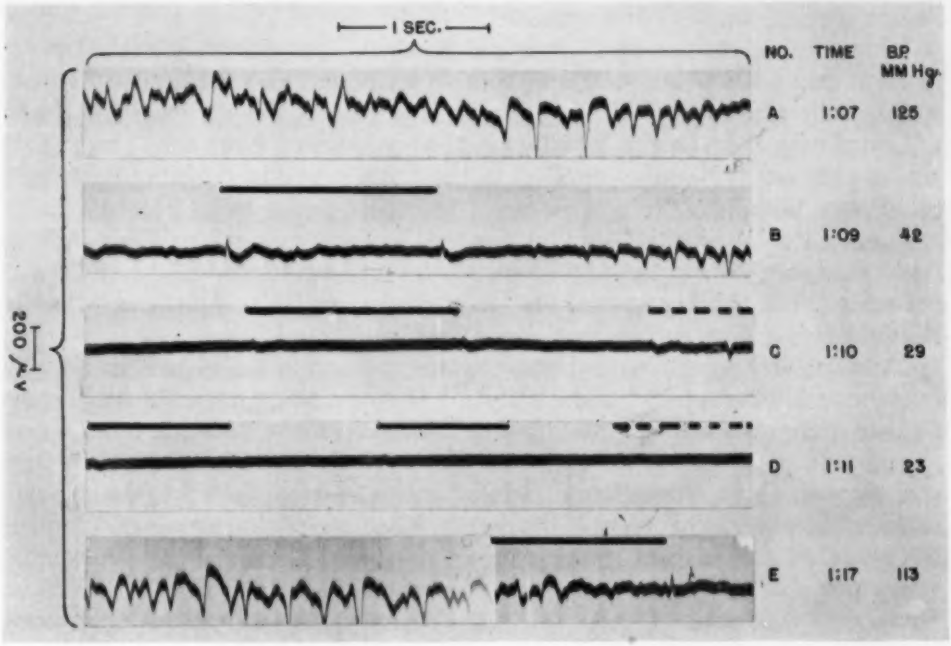

FIG. 6. Pentobarbital anesthesia. In record D the "secondary discharge" fails to appear clearly, following sciatic stimulation.

deepening the anesthesia, and, like the effects of deep anesthesia, can be overcome by reversing the causative process. In other words, simple lowering of the blood pressure results in a reversible depression of cortical activity which is indistinguishable from that occasioned by anesthetic agents; indeed one is forced to conclude that the consequences of lowering the blood pressure, if not identical, are at least similar to those occasioned by increase in depth of anesthesia. The clinical implications of this are obvious and need not be dealt with here.

Derbyshire, Rempel, Forbes and Lambert[5] have described the cortical effects of sciatic stimulation under deep pentobarbital anesthesia and deep tribromethanol anesthesia. A small initial excursion of the base line occurs with a latency of 10 to 12 msec. after sciatic stimulation. This, it is assumed, represents the arrival in the cerebrum of the afferent volley. Under the agents

just described, as well as under asphyxia, this primary deflection is followed by a secondary excursion, with a latency of 30 to 60 msec. It may be either mono- or di-phasic, and is, under certain conditions, reversible.[5] This effect, which we now call the secondary discharge, is obtained when the recorded spontaneous cortical activity has been abolished. The phenomenon quickly fails on repeated stimulation. The effect did not appear under ether unless asphyxia was superimposed upon the anesthetic. They suggest the possibility that pentobarbital and tribromethanol suppress activity in the cortex without blocking the sensory paths leading to it, but that ether blocks these paths before cortical activity is suspended.

Unpublished studies by Forbes and Rempel, in conjunction with those of Adrian[1] and Bishop[2] suggest that this phenomenon may be a cortifugal response following arrival of the afferent impulses in the cortex. Bishop and O'Leary[2] have found a similar effect in the optic nerve. Here they report that a single maximal stimulus applied to the optic nerve in rabbits under light ether anesthesia leads to a response of the optic cortex in which they differentiate four components. The first two are di-phasic potentials. These may be fused into one, of which the first phases involve positivity of the surface of the cortex. The third component is a slow surface-negative deflection, whereas the fourth is a slow surface-positive deflection.

Adrian[1] has found in the rabbit's cortex under di-allyl barbituric acid anesthesia that electrical stimulation of the cerebral cortex causes characteristic changes in surface potentials. Weak shocks make the stimulated region negative to points a few mm. distant, although these stimulated points may still be positive to more distant points. In this case this effect is due to neurones in the superficial layers of the cortex. The form of the response is changed by repeated stimulation with stronger currents. Here the chief potential change is due to elements activated at some distance below the surface. He reports that good oxygenation of the cortex is necessary for the condition in which each wave of activity travels a little further than its predecessor. Under conditions in which the spread of waves is favored the period of stimulation may be followed by after-discharge.

Somewhat puzzling is the appearance, under ether, of the secondary discharge in response to sciatic stimulation when the blood pressure was lowered by hemorrhage (Fig. 3B). It did not appear under this agent when the blood pressure was lowered by cardiac tamponade. The secondary discharge was easily elicited by sciatic stimulation under *light* pentobarbital anesthesia, *when the blood pressure was low*. When the blood pressure was normal it has been elicited only under deep pentobarbital anesthesia.

Bremer's view[3] that the difference between ether and the barbiturate depends on ether abolishing equally all elements of sensory response, while the barbiturate acts selectively on *after-discharge* (which he relates to intercalated neurones, located in the cortical network, connecting sensory and motor elements), explains some of these facts. It probably does not account for the striking effect of secondary discharge under deep barbiturate anesthe-

sia. This effect suggests that the barbiturate blocks ordinary streams of afferent impulses, perhaps simply raises thresholds in channels of approach to the cortex and thus "puts the cortex to sleep," as evidenced by smoothed base line; and that *massive* sensory stimuli (strong shock to sciatic), by virtue of *number* of simultaneous nerve impulses, break through the partial block and initiate the cortifugal discharge (or perhaps laterally spreading discharge) which constitutes the "spike." The fact that this is not evoked when the cortex is already active (in light barbiturate anesthesia) and its immediate subsidence on rapidly repeated volleys, indicates a "line busy" effect; *i.e.*, when the mechanism is thrown into action it becomes refractory to further stimuli for nearly a second.

Summary

Concentric electrodes are described which are useful in studying the electrical changes in the brains of experimental animals. The grid lead is from a point within the cortex; the ground lead from the surface.

The typical cortical patterns found under ether and under pentobarbital anesthesia have been recorded at a constant level of anesthesia. The systemic arterial pressure has then been varied by means of cardiac tamponade and the cortical effects of this recorded.

At a constant level of anesthesia a fall in blood pressure is followed by cortical changes which are indistinguishable from those caused by an increase in the depth of anesthesia.

The similarity extends even to the appearance on sciatic stimulation of a secondary cortical discharge under pentobarbital anesthesia. Heretofore this secondary discharge had been evoked only under deep anesthesia. The phenomenon is briefly discussed.

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INHIBITION AND IMPULSE SUMMATION AT THE MAMMALIAN NEUROMUSCULAR JUNCTION

C. A. MAASKE, T. E. BOYD, AND JOHN J. BROSNAN
From the Department of Physiology and Pharmacology, Loyola University School of Medicine, Chicago

(Received for publication May 6, 1938)

IN AN early stage of curarization, voluntary muscle still responds to an isolated volley of impulses sent over its motor nerve. A second volley 0.1 to 10 secs. later evokes a weaker twitch than did the first, and within limits the weakening is progressive if the series is continued (Rosenblueth and Morison, 1937). The first volley clearly leaves an inhibitory after-effect which is capable of being summated. It is not, however, simply a prolongation of the normal refractory period. If two volleys are timed only a few msecs. apart the response is greater than a single twitch (Bremer and Titeca, 1935); and when curarization is so far advanced that a single volley fails to excite, the muscle still responds if two are delivered in rapid succession. The inhibitory after-effect is therefore preceded in time by a briefer facilitation. The latter also is capable of summation to a limited degree; but on tetanic stimulation of the nerve there is only a transient initial contraction. This is followed by Wedensky inhibition, which can be maintained indefinitely.

During the junctional depression induced by magnesium salts there is likewise a stage at which motor volleys can excite the muscle by summation but not singly. In this condition, however, no inhibitory effect has apparently been described, nor has the facilitation left by the first volley been compared to that found under curare. In the recent work on chemical transmission, it has been inferred that curare blocks by rendering the receptive substance resistant to the exciting action of acetylcholine (Dale, Feldberg and Vogt, 1936; Rosenblueth and Morison, 1937). So far as we are aware, the Mg block has not been interpreted in terms of chemical transmission. It is reversible, in the mammal, by several agents antagonistic to curare, among them eserine, ACh, and potassium (Brosnan and Boyd, 1937).

This paper includes: (1) a comparison of the effects of Mg with those of curare, in respect to facilitation and inhibition at the neuromuscular junction; (2) a study of the effects of eserine, and of depressing doses of ACh, on the course of facilitation.

PROCEDURE

Dogs under nembutal anesthesia (45 mg. per kilo) were used. The right sciatic nerve was sectioned, and one or two pairs of shielded electrodes were placed on either the peroneal or the tibial branch. The leg was immobilized by drills through the tibia. Contractions of the tibialis anticus or gastrocnemius muscle, pulling against a rubber band, were recorded, the lever excursion varying approximately in linear relation to the tension. The desired degree of depression was produced by slow intravenous administration either of $MgSO_4$, $7H_2O$, in 6.7 per cent solution, or of crude curare, 0.1 to 1.0 per cent, from a burette connected to the left femoral vein. Complete suppression of the response to single volleys usually required from 0.4 to 0.6 gm. per kilo of the Mg salt, or about 2 mg. per

kilo of the curare ordinarily used. This curare was obtained from Peruvian Indians through the courtesy of a student, Mr. E. Salomone. Another sample, from Burroughs, Wellcome and Co., showed no difference in action except in potency.

For delivering paired stimuli separated by brief measurable intervals, we used the double condenser circuit described by Bernstein (1937). Stimuli of low frequency were supplied by a neon-tube circuit.

Results

1. *The inhibitory after-effect.* Our observations on this phenomenon confirm, with respect to the curarized preparation, those of Rosenblueth and Morison (1937). If, after a period of rest, the nerve is stimulated at any frequency between 6 and 600 per min., the twitches become progressively weaker.

Fig. 1. Responses of lightly curarized muscle (tibialis anticus), after one minute of rest, to stimulation of peroneal nerve at frequency of 10 per sec.

The decline is more marked with increasing dosage of curare, or with an increase in frequency of stimulation within the range indicated. The authors cited suggest that successive quanta of acetylcholine (ACh), released at the same nerve ending, become progressively smaller. The later quanta of ACh in a series might then fall below threshold for an increasing number of muscle units. It may be pointed out, however, that the weakening of responses does not continue beyond the fifth or sixth twitch. After this, even at 10 per sec., a steady level is maintained or there is a slow rise (Fig. 1). There appears to be no direct evidence to indicate a corresponding variation in quanta of ACh. It is true that Dale, Feldberg and Vogt (1936) found a progressive diminution in the output of that substance from a perfused muscle during successive periods of stimulation of its nerve (frequency 5 to 15 per sec.). Each sample of perfusate assayed, however, contained the total amount of ACh liberated by several hundred volleys. Their data hardly justify an assumption that the second quantum falls sharply below the level of the first, particularly

under conditions of normal blood supply. The same authors found that curare does not alter the amount of ACh recovered after a given period of activity of the nerve. Any changes in quanta occurring under curare must therefore be presumed to be normal. But considering the resistance to fatigue, and the brief refractory period of the normal transmitting mechanism, it seems unlikely that a period of more than 10 secs. can normally be required, after a single impulse, for recovery to the resting state.

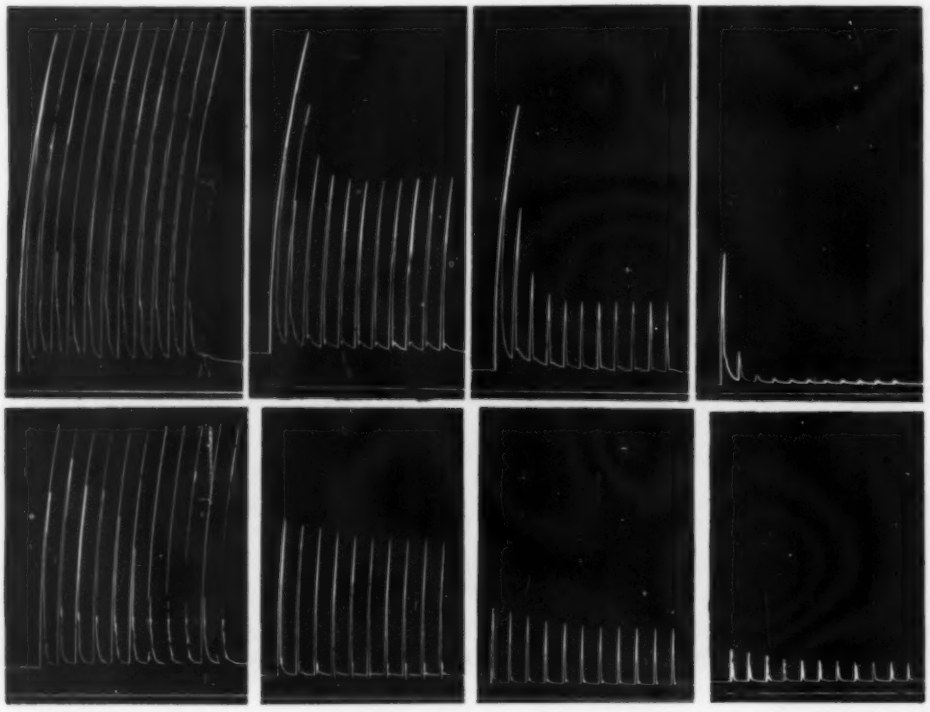

FIG. 2. Responses of m. tibialis anticus to stimulation of motor nerve, frequency 144 per min. Each series recorded after a rest of 20 secs. Showing behavior during progressive induction of junctional block by curare (above) and by $MgSO^4$ (below).

In the corresponding stages of Mg depression there is no progressive weakening in a series of twitches unless the frequency is 30 per min. or higher. Even then the decline is much smaller and more gradual than that found under curare, the difference between the first and second twitches being just perceptible (Fig. 2). Lubinska (1935) found that after the single twitch response had been suppressed by Mg, a sustained tetanus could be built up by stimulating the nerve at a frequency of 27 per sec. We have confirmed this (Brosnan and Boyd, 1936), failing to find Wedensky inhibition with any frequency up to 120 per sec. Under Mg an abrupt decline in quanta either does not occur, or it does not influence appreciably the response of the muscle. If the inhibitory

after-effect is a normal process, its time course obviously is distorted either by curare or by Mg, possibly by both.

2. *Facilitation following a single volley.* By means either of curare or of Mg, the preparation was depressed until a single stimulus to the nerve evoked a barely visible twitch. A slow inflow into the vein was then so adjusted that this minimal response was constant. Pairs of stimuli timed at varying intervals were then applied, the first of each pair being supramaximal and the second considerably stronger. When curare was used, a rest of 15 secs. was allowed between pairs of stimuli, in order to avoid the inhibitory effect. With Mg the usual interval was 10 secs. A complete time curve of facilita-

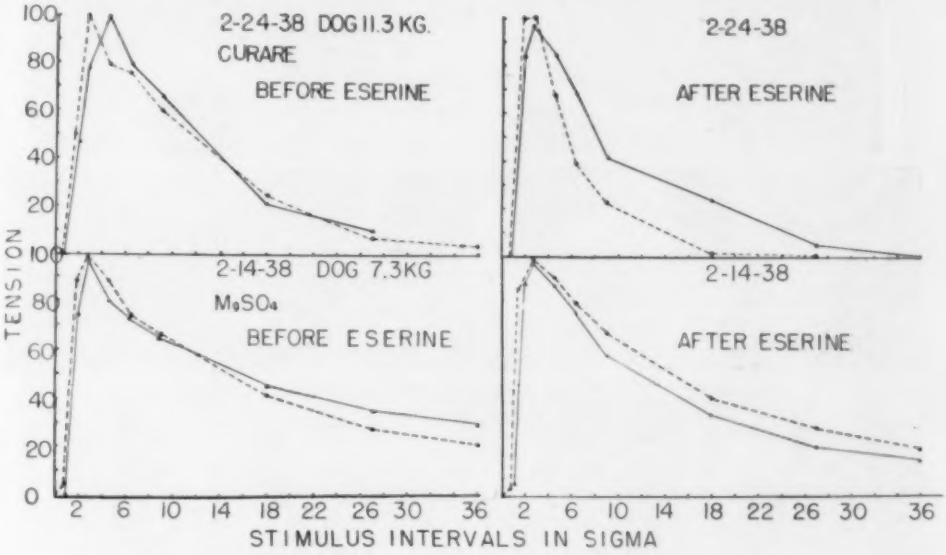

FIG. 3. Tension of summated muscle response plotted against intervals between paired stimuli, before and after eserine. Above, under curare; below, under Mg. Further explanation in text.

tion (tension plotted against time interval between first and second stimuli) was determined repeatedly on each animal, curare being used with 4 dogs and Mg with 6.

In about half the experiments, a summated response was obtained with stimuli timed only 0.9 msecs. apart. The maximum usually fell between 2 and 3 msecs. Small variations were found even when successive measurements were made on the same animal. These were probably due mainly to variations in the threshold of the nerve during the relative refractory period, and to the difficulty of maintaining a perfectly uniform state of curarization. The form of the curve is similar to that described by Bremer and Homès (1932) for the curarized frog, though the mammalian curve is briefer. Its course is approximately the same whether curare or Mg is used (Fig. 3). The rectal temperature did not vary more than 1°C. in any experiment.

3. *Absence of facilitation during Wedensky inhibition.* The lightly curarized preparation was maintained in partial or complete Wedensky inhibition by stimulating the nerve at a low frequency, 60 to 150 per min. During this time, paired stimuli 2.5 to 5.0 msecs. apart were applied through a second pair of electrodes on the nerve. The resulting response was summated either poorly or not at all, according to the degree of Wedensky inhibition existing at the time (Fig. 5A and B).

When the single twitch responses are reduced to a correspondingly low level by Mg, however, stimulation of the nerve through one pair of electrodes

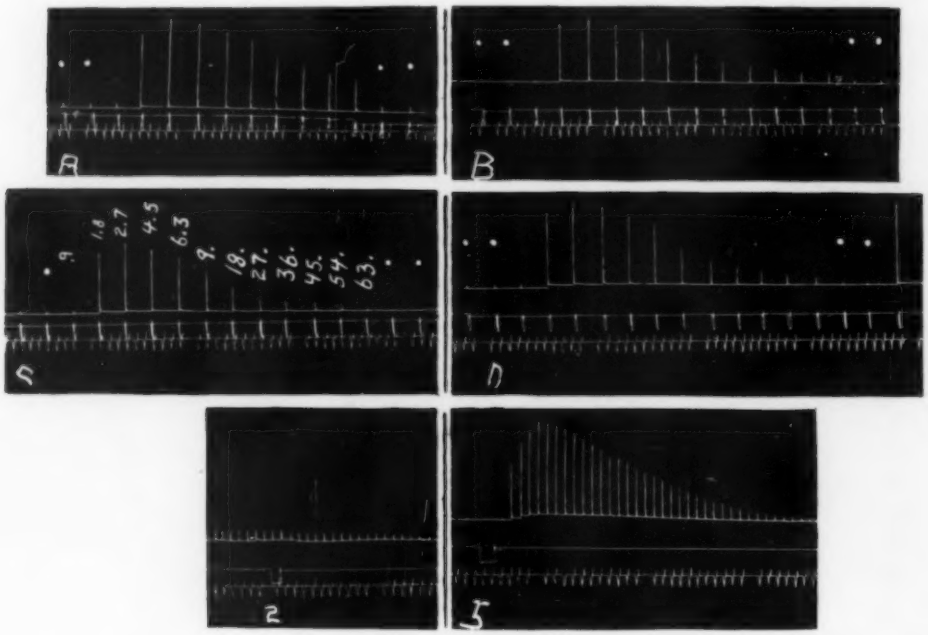

FIG. 4. Dog, 7.3 kg., nembutal, Mg. Gastrocnemius-soleus excited through tibial nerve. A and B, before eserine; C, 11 minutes after 5 mg. each of physostigmine salicylate and atrophine sulphate; D, 5 minutes after a second equal dose. Dots indicate responses to single stimuli (1 and 2) all others double. Stimulus intervals, in each series, are 0.9, 1.8, 2.7, 4.5, 6.3, 9.0, 18.0, 27.0, 36.0, and 45.0 milliseconds, in the order given. In D, the final twitch is a response to 2 stimuli 2.7 ms. apart, and duplicates the maximum of the series.

Below, same animal, single stimuli throughout at 5-second intervals. Signal 2, injection of 2 mg. of ACh, before eserine; 5, same after completion of series D above.

at the rate of 150 per min. does not prevent a summated response to two closely timed stimuli applied through a second pair of electrodes (Fig. 5C). This indicates again that the inhibitory process dominates junctional behavior under curare, but is absent or minimal under Mg.

4. *The effect upon facilitation of depressing doses of acetylcholine.* Rosenblueth, Lindsley and Morison (1936) found that acetylcholine in large doses, particularly after eserine, weakens or suppresses completely the response of muscle to indirect stimulation. If facilitation is a summation of quanta of

ACh, as suggested by Rosenblueth and Morison (1937), paired stimuli, applied to the nerve during this depression, should be no more effective in exciting the muscle than single shocks; for any ACh released by the first volley of impulses would add to the depressing concentration already existing.

We first administered eserine (0.5 to 1.0 mg. per kilo). This caused the usual potentiation of twitch responses to single volleys at 8 to 10 sec. intervals. At such a slow frequency of stimulation we were unable to suppress the twitch responses completely by any dosage of ACh up to 1 mg. per kilo (intravenous). On increasing the frequency of test stimuli to 2 per sec., the

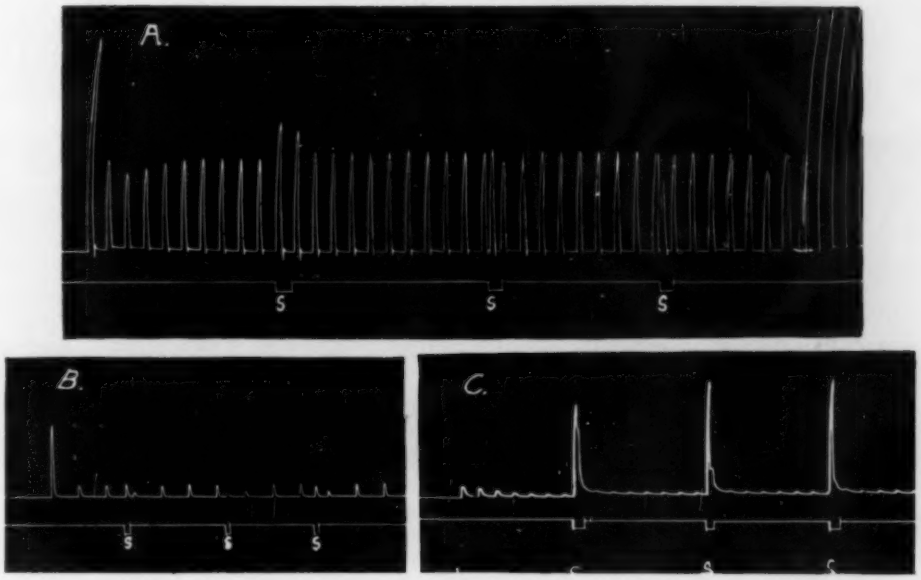

FIG. 5. Paired stimuli 2.7 milliseconds apart applied to peroneal nerve at down stroke of each signal, while low-frequency stimulation was being maintained through a second pair of electrodes. A, in early curarization; B, same animal, deeper curarization; C, another animal, after twitch responses had been nearly suppressed by $MgSO_4$. Twitch frequencies, in A, 3 per sec., in B, 1, and in C, 2.5 per sec. Summation well marked in C, feeble in A, absent in B.

twitches were nearly or completely suppressed; and during the depression two closely timed stimuli applied through a second pair of electrodes failed to evoke a summated response (Fig. 6). This is perhaps negative evidence in favor of the theory that facilitation is a summation of quanta of ACh; but as shown above, the curarized preparation behaves in the same way under similar conditions of stimulation. In both conditions, the absence of facilitation is associated with a low-frequency Wedensky inhibition.

5. *The effect of eserine on the time course of facilitation.* After carrying out the procedure described in section 2 above, we administered to the same animals 0.5 mg. per kilo of physostigmine salicylate, with an equal dose of atropine sulphate. This decurarized, but the original state of block was re-

stored by administering additional Mg or curare. The time curve of facilitation was then again determined. Typical curves are shown in Fig. 3, and graphic records in Fig. 4. In a few instances the period of effective summation was found shorter after eserine than before; usually the two curves nearly coincided. Once the maximum fell later (at 4.5 ms.) after eserine than before (3.0 ms.) but the descending portion of the curve was never prolonged. We found, though not constantly, the shortening of the minimum summation interval noted by Bremer and Kleyntjens (1937).

The last-named authors report that eserine does not prolong the period of impulse summation in the curarized frog. Eccles (1935) had previously reported a failure of eserine to prolong facilitation in the superior cervical ganglion of the cat, and concluded that summation of quanta of ACh could not be the mechanism of facilitation in the ganglionic synapses. Cannon and Rosen-

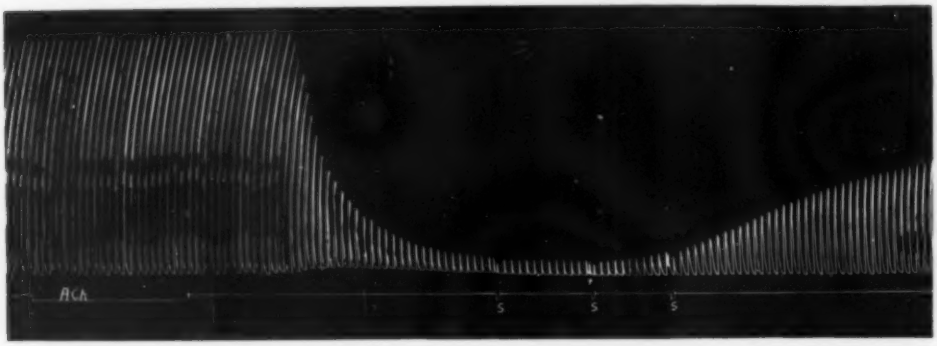

FIG. 6. Dog, 14.5 kg., nembutal. Eserine and atropine (7 mg. of each) 7 minutes before beginning of record. Twitches of m. tibialis anticus, in response to stimulation of peroneal nerve at frequency of 2 per second. *ACh*, intravenous injection of acetylcholine, 4 mg. At each signal S, paired stimuli 4.5 milliseconds apart were applied through a second pair of electrodes.

blueth (1937) object to this conclusion, on the ground that Eccles' records may have been made after an interval long enough for the anticholinesterase activity of the eserine to have disappeared. In the experiments of Bremer and Kleyntjens, a single dose of curare was administered to each frog. When the desired stage of curarization had been reached, the time curve of facilitation was determined. Eserine was then administered, with a temporary decurarizing effect; but the preparation soon lapsed into the original state of curarization and the records were repeated. The authors assume that the return of junctional block after eserine was not due to disappearance of the effect of that agent, but to a continued progressive action of the curare. While this assumption may have been correct, it would seem desirable to supply more direct evidence about the duration of the effect of eserine.

In our experiments, a period of 10 to 25 mins. elapsed, after eserine, before the animal was recurarized to the desired constant state. A second equal dose of eserine could then be given, however, with little or no decurarizing action.

As a routine, we made one series of records of facilitation after the first dose of eserine, and repeated the procedure within 10 minutes after the second dose. Both sets of records thus obtained were quite similar to those made before eserine (Figs. 3 and 4). Finally, we regularly administered two equal doses of ACh, 0.2 to 0.4 mg. per kilo, one before eserine and the other after completing the final series of facilitation records. The decurarizing action of the second dose was always greater and more prolonged than that of the first (Fig. 4).

Discussion

It seems to us that latent addition at the neuromuscular junction cannot be attributed to summation of quanta of ACh. The question is discussed at length by Bremer and Kleyntjens (1937) who suggest that the first blocked impulse sets up a subliminal excitatory state in the muscle; that this excitatory state dies away gradually, and while it persists may be raised to threshold value if a second similar process is superimposed. The authors cited consider that this view is compatible with the theory that acetylcholine is the essential transmitter, since the cellular excitatory process might be set up by a quantum of ACh. But eserine restores the response of the curarized preparation to a single volley. If this effect is due to its anticholinesterase activity, it follows that the excitatory state assumed by Bremer and Kleyntjens varies in intensity according to the amount of ACh acting; and it is still difficult to see why eserine should not prolong the period of facilitation, unless the destruction of each quantum of ACh is so rapid that summation, even after eserine, is impossible.

It may be objected that in our experiments (also in those of Bremer and Kleyntjens) recurarization after eserine raised the threshold of the muscle for ACh; and that although the period for summation of two quanta may actually have been prolonged, this effect was nullified because summation had to reach a higher level than before in order to excite the muscle. Such an objection, however, can hardly be maintained. If the threshold was raised by the additional curare or Mg, eserine had also raised the level reached by a single quantum, so that the relation between the first quantum and the threshold was the same as before. The increment added by the second quantum must have been correspondingly increased after eserine, so that it should have reached threshold value so long as any considerable residue was left from the first. This presumes that the first and second quanta are equal, or nearly so. If the second is much smaller than the first, as Rosenblueth and Morison suggest, comparison of the facilitation curves before and after eserine becomes more complicated; but as was pointed out in section 1 above, there is no convincing evidence that such a disparity exists.

We have used the terms "impulse summation" and "facilitation" interchangeably. Bremer and Kleyntjens (1934) use the latter term to designate an enduring after-effect of manifest activity in synapses; the former they apply to a subthreshold junctional effect left by one or more impulses which fail to be transmitted. Impulse summation or latent addition they consider to

be a relatively brief process. But such a distinction is difficult to apply to the neuromuscular junction. Tetanic stimulation of a motor nerve in the curarized mammal may fail to excite the muscle, and yet leave a facilitation lasting for several minutes (Boyd, 1932).

Summary

1. When the nerve of a lightly curarized mammalian preparation is stimulated at any frequency from 6 to 600 per min., the second muscle twitch is weaker than the first and a sustained Wedensky inhibition of some degree follows (confirming Rosenblueth and Morison).

2. During corresponding stages of neuromuscular depression produced by magnesium salts, the inhibitory effect of repeated stimulation is much less in degree, and of shorter duration, than under curare.

3. When the response to a single volley of impulses has been completely suppressed by Mg, the muscle can still be excited if two stimuli are applied to the nerve in rapid succession. The junctional summation of the two volleys follows a time course closely resembling that found under curare.

4. The depression of neuromuscular transmission produced by excessive concentrations of acetylcholine is a low-frequency Wedensky inhibition, resembling in its time relations that of the lightly curarized preparation. In both of these conditions junctional summation of two closely timed volleys is ineffective. During Mg depression, however, low-frequency stimulation of the nerve at one point does not prevent a summated response to two volleys set up elsewhere on the nerve.

5. Under curare, the period for effective junctional summation of two volleys is not prolonged following administration of eserine, with recurarization to the original state of block (confirming Bremer and Kleyntjens). The result is also negative if Mg is substituted for curare. The failure of eserine to prolong the summation period is not due to rapid disappearance of its anticholinesterase activity.

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AUTONOMIC ACTIVITY AND BRAIN POTENTIALS ASSOCIATED WITH "VOLUNTARY" CONTROL OF THE PILOMOTORS (*MM. ARRECTORES PILORUM*)

DONALD B. LINDSLEY AND WILLIAM H. SASSAMAN
Laboratory of Anatomy and Associated Foundations, Western Reserve University, Cleveland, Ohio

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THE CONTROL of most of the functions of the autonomic nervous system is generally considered to be "involuntary" in character. A few cases have been described, however, in which one or another of the autonomic activities is under "voluntary" control. Most of these deal with some aspect of the visual mechanism, such as, "voluntary" control of accommodation,[2,3,16,17] pupillary dilatation[14] and constriction.[11] The case to be described here is of particular interest since it involves "voluntary" control of the *arrectores pilorum* muscles which are innervated only by the sympathetic division of the autonomic nervous system.

The subject is a middle-aged male, who since the age of 10 years has been aware of the ability to control the erection of hairs over the entire surface of his body. Experimental study of the subject has revealed that the erection of hairs is accompanied by a number of other autonomic phenomena of which he was not aware. These consist of an increase in heart rate, an increase in the rate and depth of respiration, dilatation of the pupils, an increase in the electrical potentials of the skin over regions rich in sweat glands and characteristic changes in the electrical potentials over the premotor area of the brain.

METHODS

Sixteen millimeter motion picture records, at a measured speed of 18 frames per second, were made of the erection of the hair on the dorsal surface of the forearm, the lateral surface of the thigh, and the anterior surface of the leg just below the knee. Similar records of the dilatation of the pupil, which occurs during "voluntary" erection of the hair, were made while the eye was illuminated by a 500 watt flood lamp at an angle of approximately 45° to the anterior surface of the cornea. Fixation of the eyes was always maintained on a point 15 feet away. A quick movement of the experimenter's hand before the lens of the camera marked the film and served as a signal for the subject to begin the erection of the hair; the same movement repeated meant to lower the hair. The movement fell on the periphery of the visual field and did not intercept the line of regard. The signals used in other aspects of the study consisted of a barely audible "click" in a headphone and the "flash" of a dim light. Control experiments in every case indicated that none of the effects observed was due to the stimulus value of the signals themselves.

Simultaneous recording of electrical phenomena, such as the electrocardiogram and skin potentials, or brain potentials from two regions on the surface of the head, was accomplished by means of two independent amplifying and recording systems. The amplifiers are of the resistance-capacity coupled type, with pre-amplifiers employing balanced input circuits. The time-constant of the amplifiers may be made appropriate to the particular type of phenomena to be recorded by changing the inter-stage coupling capacity (0.1, 0.5, or 2.0 mfd.). A type-PA Westinghouse oscillograph with matched elements served as the recording unit. The mechanical devices for recording respiration and changes in blood pressure are incorporated in the oscillograph case so that all phenomena may be recorded simultaneously on the same record if desired. Continuous changes in blood pres-

sure were recorded with the pressure in the cuff on the arm maintained at 70 to 80 mm. of Hg for short periods of time. Systolic and diastolic readings by the auscultatory method were also made before and during the erection of the hair.

Electrodes for recording brain and skin potentials consisted of small gold discs, 8 mm. in diameter, each sunk in a small bakelite block. The cup of the block was filled with an electrode jelly which served as the conducting medium. When brain potentials were recorded the electrodes were attached to the surface of the scalp, one to two inches apart, and held in place by bandages. For the recording of skin potentials the electrodes were attached to the palmar surface of the hand. Small silver plates and electrode jelly applied to the left wrist and ankle furnished leads for the electrocardiogram. Electrograms from individual arrectores pilorum muscles were obtained by means of needle electrodes inserted through the skin at the base of a hair on the side toward which it leaned. The needle electrodes consisted of a fine gauge hypodermic needle with either one or two fine insulated wires cemented in its lumen. When the first type was used the exposed tip of the single inner wire led to grid and the sheath of the needle to ground; in the latter case the exposed tips of the two wires led to the balanced input of a pre-amplifier and the sheath of the needle was grounded.

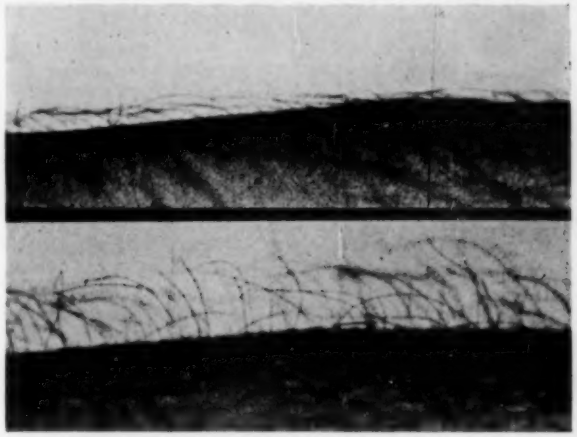

FIG. 1. "Voluntary" erection of the body hairs. Sections from a motion picture record of the hair on the lateral surface of the thigh, before the signal to erect the hairs and about 10 seconds after the signal showing the hairs erect and the "gooseflesh" appearance of the skin.

RESULTS

Several series of experiments have been made in which the erection of the hair on the arms and legs was photographed. Fig. 1 shows two frames from a motion picture record of the erection of the hair on the thigh. The first shows the hair in its normal position close to the surface of the skin before the signal to erect the hairs. The second, taken approximately 10 secs. after the signal, shows the hairs almost fully erected and the "gooseflesh" appearance of the surface of the skin.

Fig. 2 shows three frames from a motion picture record of the dilatation of the pupil which accompanies the "voluntary" erection of the hairs. The first is from a section of the record before the signal to erect the hairs and shows the pupil well constricted. The second shows the increased diameter of the pupil while the hairs are erect; the third shows the decreased diameter

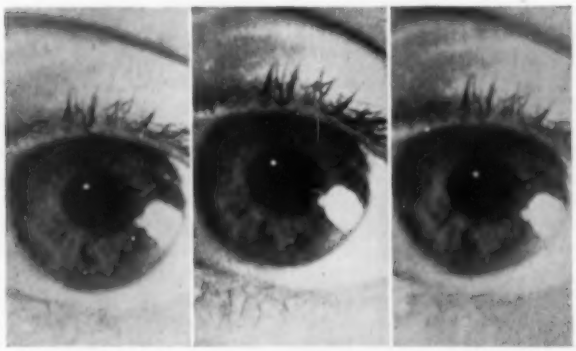

FIG. 2. Dilatation of the pupil during "voluntary" erection of the body hairs. Sections from a motion picture record before, during and after the erection of the hairs.

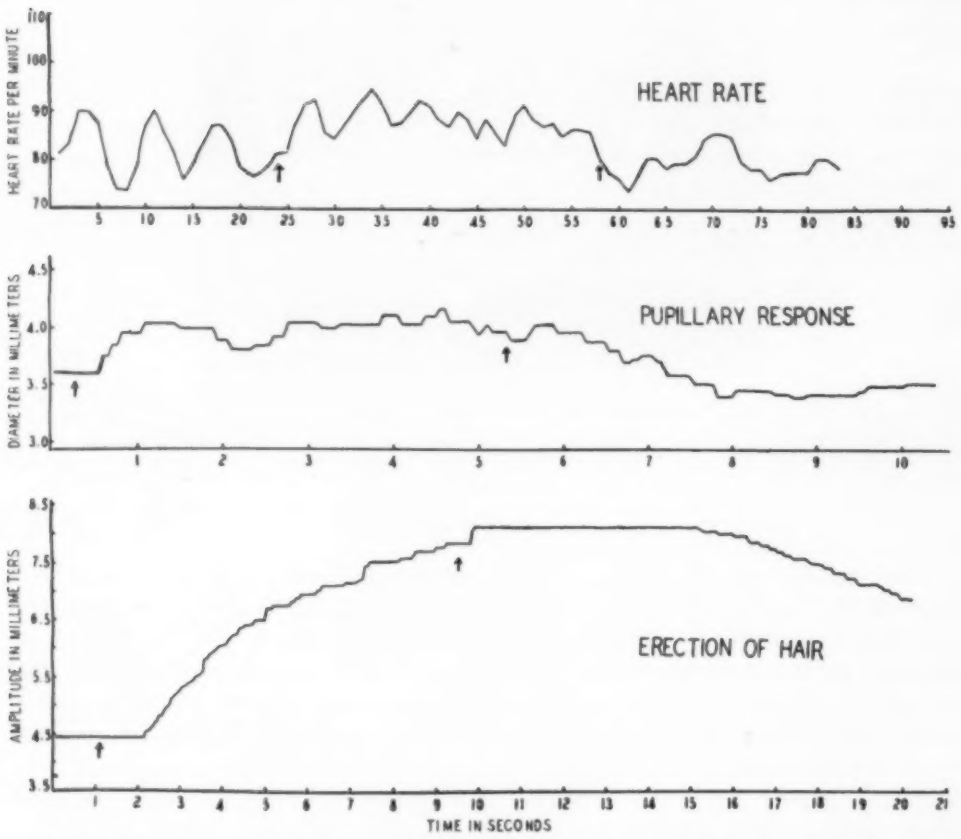

FIG. 3. Graphs showing changes in the heart rate, diameter of the pupil and the distance of a hair from the surface of the skin following a signal (first arrow) to erect the hairs and a signal (second arrow) to lower them.

a few seconds after the signal to lower the hairs. Frame by frame analysis of the motion picture records under magnification in an Edinger projector revealed that the hairs began to rise approximately 1 sec. after the signal was given. By plotting the distance of the tip of any hair from the surface of the skin in successive frames (see Fig. 3) it was found that the erection of a hair proceeds in a step-wise fashion. Maximum elevation of a number of hairs studied was attained in about 7 secs. After a signal to lower the hairs was given 5 to 6 secs. elapsed before actual lowering occurred. The lowering of the hairs also proceeded by steps and was completely accomplished between 15 to 20 secs. after the signal to lower them.

The degree of illumination necessary for photographing the pupils caused considerable constriction which competed with the dilatation accompanying

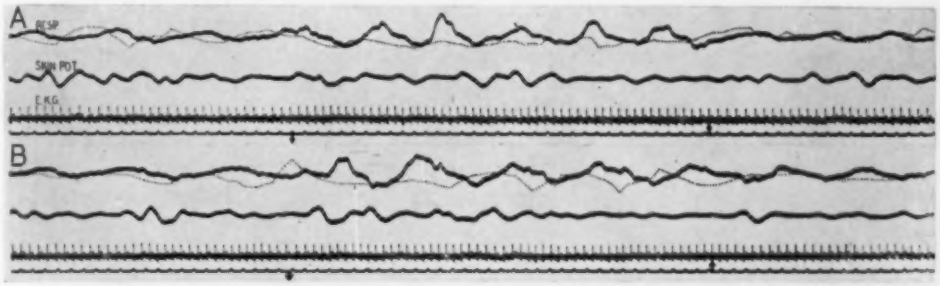

FIG. 4. Simultaneous records of heart rate (E.K.G.), respiration and skin potentials from the palm of the hand showing distinct changes during the "voluntary" erection of the body hairs. The dotted line is a continuous record of changes in heart rate; an increasing rate is shown by a descent of the line. The first arrow represents the signal to erect the hairs, the second to lower them. Time is shown in seconds at the bottom of each record.

the "voluntary" erection of the hairs. The pupils at the start of an experiment usually ranged from 3 to 3.5 mm. in diameter. Dilatation of the pupils (see Fig. 3) began 0.3 to 0.5 of a sec. after the signal to raise the hairs. Maximum enlargement of the diameter under these conditions of high illumination ranged from 0.5 to 1.5 mm. and was usually attained in 0.5 of a sec. Enlargement of the pupils was maintained throughout the duration of the erection of the hairs at a level well above the starting diameter, although there were frequent fluctuations due to the competing tendencies for dilatation and constriction. Five-tenths of a sec. after the signal to lower the hairs the pupils began to constrict in a step-wise manner. Constriction always proceeded to a level below that of the original diameter of the pupils but slowly returned to it.

Simultaneous records of heart rate (electrocardiogram), respiration and skin potentials from the palm of the hand (see Fig. 4) show that changes in these phenomena occurred approximately 1 sec. after the signal to erect the hairs. The dotted line in these records gives moment to moment heart rate values which were obtained by measuring the interval between successive R-waves of the electrocardiogram with proportional dividers adjusted to mul-

tiply by 10 and erecting an ordinate over the midpoint of each interval. A typical curve of heart rate changes during the erection of the hairs is shown in Fig. 3. Heart rate, which oscillates widely during the two phases of respiration, was maintained at a definitely higher level while the hairs were erect than before they were raised or after they were lowered. During the "voluntary" erection of the hairs the heart rate was increased by 6 to 8 per cent; respiration was increased by 9 to 25 per cent in rate and by approximately 100 per cent in depth. Anticipation of the signal frequently increased the skin potentials in the palm of the hand but the degree of activity was usually distinctly increased about 1 sec. after the signal to raise the hairs.

Fig. 5 shows electrograms obtained from individual arrectores pilorum muscles by means of needle electrodes during the "voluntary" erection of

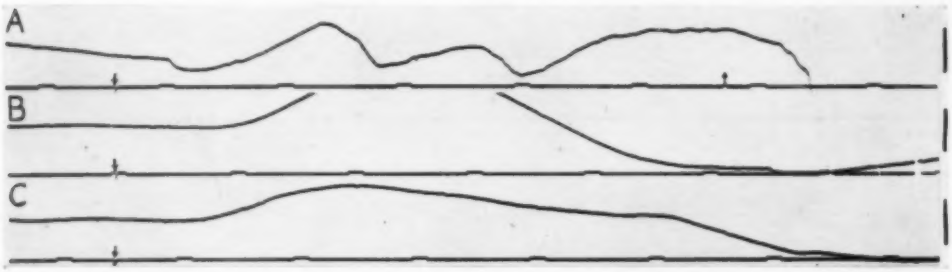

FIG. 5. Electrograms from individual arrectores pilorum muscles during "voluntary" elevation of the body hairs. The first arrow indicates the signal to erect the hairs, the second to lower them. Time is shown in seconds at the bottom of each record. Calibrations at right of each record equal 150 microvolts.

the hairs. The electric response occurs from 0.5 to 0.7 of a sec. after the signal to raise the hairs and thus precedes the mechanical movement of the hairs which has a latency of about 1 sec. As shown in Fig. 5, the electric response may consist of rhythmic oscillations (A), or long, slow undulations (B and C). Occasionally small, quick, spike-like components are superimposed. Both the rhythmic and the more prolonged electric responses have been described in smooth muscle by Lambert and Rosenblueth,[13] Rosenblueth, Davis and Rempel,[15] and by Eccles and Magladery.[6,7] The electric responses shown here seem to correspond in time relations to the slow component III described by Lambert and Rosenblueth,[13] but there is no "initial complex" corresponding to their components I and II. Since, for the purposes of this study, latency is the main concern, further analysis of the response will not be attempted here.

Continuous records of the relative changes in blood pressure have shown that there is a very slight increase during the "voluntary" erection of the hairs. Repeated readings by the auscultatory method have shown that there are also very slight elevations of the diastolic and systolic pressures. Although the changes were always in the direction of an increase they have for the most part been too small to be considered significant.

Electrical potentials of the brain were recorded simultaneously from over two regions of the same hemisphere during "voluntary" erection of the hairs, usually from the premotor and occipital, premotor and temporal, premotor and parietal, or the premotor and the anterior part of the frontal region. Characteristic responses consisting of large, slow waves were found only over the premotor region (see Fig. 6). The latency of the electric response of the premotor region ranges from 0.23 to 0.35 of a sec. There is sometimes an "off response" 0.2 to 0.3 of a sec. after the signal to lower the hairs. The general pattern of the premotor response is essentially the same on repetition of the experiment. The largest response is obtained when the electrodes are over a region just anterior to the central sulcus, in a line parallel with, but about 1 inch off the mid-line. According to careful estimate by Chiene's

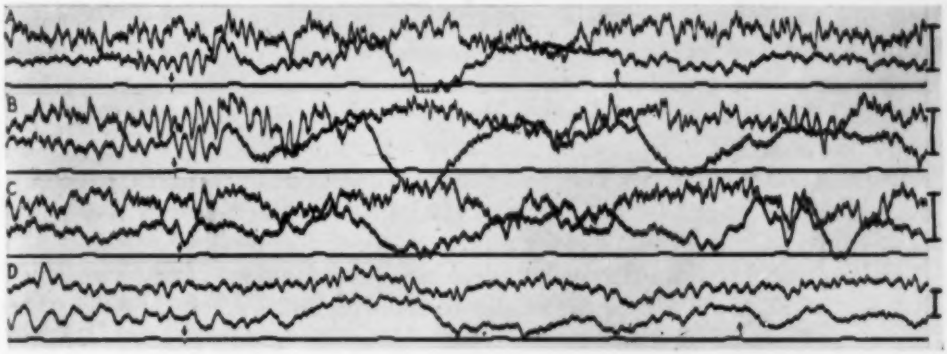

FIG. 6. Electrical potentials of the brain simultaneously recorded from over the premotor (middle line of each record) and occipital (upper line) areas during "voluntary" erection of the hairs. In A, B, and C the premotor electrodes were over the upper part of 6aα; in D they were over the upper part of 6aβ. The first arrow indicates the signal to erect the hairs, the second to lower them. Time is given in seconds at the bottom of each record. Calibrations at the right of each record equal 20 microvolts.

method[5] for determining the relationship between cranio-cerebral topography, the area between the electrodes probably included, mainly, the upper part of area 6aα and parts of areas 4 and 6aβ. Responses were obtained from over the outlying regions of 6aα and 6aβ but they were never as prominent as those from the upper part of 6aα.

The nature and direction of the various changes in autonomic activity associated with the "voluntary" erection of the hairs, together with the general concurrence of these changes suggest that there is a generalized sympathetic discharge. The fact that marked changes in the brain potentials occur only over the premotor area and precede the peripheral autonomic phenomena further suggests that the premotor cortex plays a part in the generalized sympathetic discharge associated with the "voluntary" erection of the body hairs.

DISCUSSION

The question arises as to how the subject is able to control the erection of the body hairs. So far as he is aware the process is essentially similar to

that of initiating contraction in one of his skeletal muscles. He does not call up an image of a painful or fearful experience as has been reported in connection with one case of so-called "voluntary" control of pupillary dilatation.[14] There is no straining or tensing of skeletal muscles and there are no observable movements of any sort. The subject is able to erect the hairs when in any position and while carrying on other activities. Of special importance is the fact that he is able to inhibit the reflex erection of the hairs and the appearance of "gooseflesh" normally induced by stepping out of a hot shower into a cold draft.

In this case, as in some of the others which have been described, "voluntary" control of an autonomic function was first discovered during childhood; either during severe fatigue, a critical illness or some other unusual condition. It may be that, unknown to these subjects, some form of conditioning took place when, under unusual circumstances, their attention was first called to the reflex manifestation of an autonomic function. Cason[4] and Hudgins[11] have shown that pupillary constriction may be conditioned to an auditory stimulus. Hudgins has even demonstrated that pupillary constriction originally induced by a light stimulus may be conditioned to the command "constrict" or even to the subvocal production of verbal stimuli by the subject himself. This has led Hunter and Hudgins[12] to offer the hypothesis that all so-called voluntary behavior is a form of conditioned response.

With respect to the subject described here there is no satisfactory evidence that he did not always have the ability to erect the hairs nor is there evidence that some form of conditioning took place when he first noticed the ability.

No matter how the "voluntary" control of the pilomotors is brought about in this case the familiar tendency of the sympathetic system to respond as a whole is apparent in the accompanying phenomena. The latencies of these various responses are of such an order as to indicate that they are a part of a generalized discharge of the sympathetic system. The finding of characteristic brain potential changes over the premotor area suggests that they are precursors of the peripheral autonomic changes. This corresponds with the results from experiments on animals[8,9,10,18] and human subjects[1] which have indicated that there is an autonomic representation in the cortex, particularly in the premotor area.

Summary

A subject has been described who has "voluntary" control of the pilomotors (*arrectores pilorum* muscles). Experimental study of the subject has revealed that the "voluntary" erection of the body hairs is accompanied by an increase in heart rate, an increase in the rate and depth of respiration, dilatation of the pupils, an increase in the electrical potentials of the skin over regions rich in sweat glands, and a very slight increase in blood pressure. The nature and direction of these changes together with their latencies indicate a tendency for a generalized sympathetic discharge.

Simultaneous records of electrical potentials from two regions of the brain,

the premotor and one of the other regions, during the "voluntary" erection of the body hairs have shown characteristic changes only over the premotor area. These premotor responses precede and appear to be associated with the peripheral autonomic changes. This has been interpreted as further evidence of the representation of the autonomic nervous system in the premotor area of the cortex.

The possibility that the subject's ability to control the erection of the hairs is the result of a conditioning process has been discussed, but no satisfactory evidence for or against this hypothesis is at hand.

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THE INFLUENCE OF HYPOTHALAMIC STIMULATION ON INTESTINAL ACTIVITY

JULES H. MASSERMAN AND E. W. HAERTIG
From the Division of Psychiatry and The Otho S. A. Sprague Memorial Institute, University of Chicago, Chicago

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IT IS the purpose of this study to investigate the functions of the hypothalamus in regulating the motility and blood supply of the small intestine in relation to the other vegetative, emotional and mimetic reactions produced by the electrical stimulation of the diencephalon, or by the injection of strychnine sulphate into its nuclei.

METHODS*

Fourteen cats were prepared in two series of experiments as follows:

Acute experiments (8 animals). The experiment was usually performed approximately 6 hours after the animal had been fed. Ether anesthesia through an intratracheal cannula was maintained at a level just deep enough to abolish spontaneous movements. With the Horsley-Clarke stereotaxic instrument† in place and an electrode inserted into the hypothalamus, the animal was mounted in an upright position in a hammock provided with holes for the legs and the exposed gut. The blood pressure in the right common carotid artery and the respirations were recorded on a kymograph in the usual manner above the tracings of a signal magnet and a one-second timer. A wide, shallow beaker containing Ringer's solution kept at a temperature of about 39°C. was then arranged so that the dependent portions of the jejunum and ileum were supported just outside the incised and dorsally displaced abdominal wall, thus preventing traction on the mesentery and interference with the blood supply of the intestines. Under these conditions, peristalsis, rhythmic segmentation and pendular movements of the gut were easily observed, although in some animals the small intestine seemed entirely motionless for varying periods. The animal's temperature was maintained at a normal level by warming the Ringer's solution continuously and by the use of an electric heating pad applied to the animal's back when necessary. Cats prepared in this manner remained in good condition for as long as 5 hours with little change in reactivity to repeated electrical stimulation of the hypothalamus except as induced by the administration of strychnine.

Recovery experiments (6 animals—23 experiments). In a cat anesthetized with pentobarbital sodium, a bipolar needle electrode was inserted by means of the Horsley-Clarke stereotaxic instrument into the hypothalamus and then firmly cemented in position to the skull. In 8 to 24 hours the animal usually recovered completely from the operation and could then be observed in an unanesthetized, untrammelled state for the effects of electrical stimulation of the hypothalamus before or after the injection of this structure with solutions of strychnine sulphate or other substances. In preparation for fluoroscopy, the animal was given 100 cc. of an opaque mixture (barium sulphate suspended by mucilage

* The various techniques employed in preparing animals for the stimulation or injection of the diencephalon have been described in detail in earlier communications from this laboratory. See MASSERMAN. J. H.: Effects of sodium amytal and other drugs on the reactivity of the hypothalamus of the cat. *Arch. Neurol. Psychiat., Chicago*, 1937, *37:* 617–628. MASSERMAN, J. H.: The effects of the destruction of the hypothalamus of the cat on its activity and on the pharmacologic action of sodium amytal. *Arch. Neurol. Psychiat., Chicago.* In press.

† HORSLEY, V., and CLARKE, R. H.: The structure and functions of the cerebellum examined by a new method, *Brain*, 1908, *31:* 45–124. CLARKE, R. H., and HENDERSON, E. E.: *Investigations of the central nervous system: methods and instruments.* Baltimore, Johns Hopkins Press, 1920. RANSON, S. W.: On the use of the Horsley-Clarke stereotaxic instrument, *Psychiat. en neurol. bl.* (Feestb. C. H. Ariëns Kappers), 1934, *38:* 534–547 (May-Aug.).

of acacia in water) from 30 to 60 minutes before experimental observations were made. Fluoroscopy was done approximately 24 hours after operation and again after 48 hours if the animal's rectal temperature had not reached 105°F. At the time of the first examination the pyloric antrum and the entire small intestine were usually well visualized and showed active rhythmic segmentation and peristalsis.

Stimulation. For electrical stimulation of the hypothalamus, a Harvard inductorium carrying three volts across the terminals of the primary coil or a 60 cycle alternating current reduced by a series of variable resistances to from 0.5 to 9.0 volts was employed. The effects of bipolar (highly localized) and unipolar (diffusing) stimuli were observed before and after the injection of strychnine sulphate into the hypothalamus in both acute and recovery preparations.

Injections. Selected amounts of strychnine sulphate were dissolved in 0.05 to 0.1 cc. of water and injected into the hypothalamus at the rate of 0.1 cc. per min. Dosages of from 0.07 to 0.20 mg. per kilogram were given, the smaller dosages usually being repeated in from 30 to 60 minutes.

Anatomic studies. After the terminal experiment the brain was fixed in a 10 per cent solution of formaldehyde and the region of the hypothalamus sectioned serially and stained in alternate sections for nerve fibers by a modified Weil technique and for nerve cells by the Nissl method. The sections were then examined to determine accurately the nerve structures that had been stimulated and injected.

Sites of stimulation and injection. Most of the observations (7 animals in the acute series, and all 6 of the recovery preparations) were made with the electrode at coordinate settings of from 2.0 to 2.5 mm. to the right of the midline, from 10.0 to 12.5 mm. anterior to the interaural frontal plane and from 4.0 to 6.0 mm. below the zero horizontal plane of the stereotaxic apparatus. The structures directly affected by stimulation and injection were: the rostral tip of the H_1 field of Forel, a portion of the substantia nigra, the lateral margin of the nucleus filiformis principalis, the nucleus perifornicalis, the nucleus hypothalamicus anterior, the upper and lateral edge of the nucleus supra-opticus diffusus, the dorsal hypothalamic area and the rostral one-third of the nucleus hypothalamicus lateralis.* In 5 animals, the same region in the left hypothalamus was also studied and in a number of others more extensive explorations were made in structures that will be specified when the results of stimulation and injection are described.

Results

Acute experiments

In animals anesthetized with ether the average strengths of current necessary to produce responses to stimulation of the hypothalamus were obtained at the secondary coil setting of 10 cm. on the Harvard inductorium or at AC voltages of 3.0 V. for bipolar and 2.0 V. for unipolar stimulation. When these stimuli were employed in animals in which the exposed gut had been quiescent, rhythmic segmentation and peristalsis appeared in about 5 secs. and persisted for about 10 secs. after the period of stimulation (usually 15 secs.) was terminated; this series of responses could be elicited repeatedly. In addition, pendular, swaying and coiling movements of the gut with almost identical periods of latency and persistence were initiated by hypothalamic stimulation in seven animals and augmented when spontaneously present in one. Segmentation and peristalsis usually appeared and disappeared together, but the pendular movements could be elicited independently. However, in

* The anatomic terminology used throughout this paper is adopted from Ingram, W. R., Hannett, F. I., and Ranson, S. W.: The topography of the nuclei of the diencephalon of the cat, *J. comp. Neurol.*, 1932, *55:* 333–394. More extensive charts of the Horsley-Clarke coordinates of anatomic structures may be found in Clarke, R. H., and Henderson, E. E.: Atlas of photographs of sections of frozen cranium and brain of the cat, *J. Psychiat. Neurol., Lpz.*, 1911–12, *8:* 119–156.

no instance were rhythmic segmentation, peristalsis, or pendular movements diminished by stimulation in this region of the hypothalamus with the strengths of current specified nor did the general tonicity of the small intestine seem to be affected. Both dilatation and constriction of the blood vessels in the intestine were observed to follow stimulation of the hypothalamus in various experiments, but more frequently there were no visible changes and cyanosis was never produced.

General effects. Accompanying these enteric reactions were other evidences of mild autonomic stimulation: partial dilatation of the pupils, contraction of the nictitating membranes, widening of the palpebral fissures, an elevation in blood pressure of from 5 to 30 mm. of mercury and an increase in the rate and depth of the respiration. Responses of the skeletal musculature consisted in slight movements of one or more of the extremities, twitching of the ears, closure of the jaws and occasionally, torsion of the head and neck. These bodily movements sometimes slightly displaced the intestines, but segmentation, peristalsis, and pendular movements in the absence of hypothalamic stimulation were not induced by respiratory excursions nor by moving the gut loops about in the beaker.

Stimulation of other regions of the diencephalon and mesencephalon. Segmentation and peristalsis of the intestine could be elicited by stimulating either side of the tuber cinereum or the dorsal portion of the supramammillary decussation. Similarly, pendular movements were induced or enhanced by stimulation in and above the middle portions of the mammillary bodies and in the supramammillary decussation and its nucleus. In contrast, diminution or abolition of intestinal movements followed stimulation with relatively weak currents in the suprachiasmic region and in the supramammillary decussation 2 mm. below the point at which pendular movements had been obtained. Stimulation in the suprachiasmic region also led to generalized spasticity and blanching of all of the visible intestinal loops—an effect which, in some animals, persisted until stimulation in the tuber cinereum brought a return of activity. Dilatation of the intestine was not observed in any of the experiments.

Effects of stronger stimuli. When the hypothalamus was stimulated with currents intense enough to elicit marked emotional mimetic responses (secondary coil settings of 8 to 7 cm. or 6 to 7 volts AC for bipolar and 3 to 4 volts for unipolar stimulation) intestinal motility, when spontaneously present, was either definitely reduced or stopped during the period of stimulation and for several minutes thereafter. In animals in which the gut had been motionless before stimulation of the hypothalamus with these strengths of current, no activity appeared during or following the stimulus, even though weaker currents applied to the same point in the hypothalamus had previously been effective in eliciting vigorous intestinal movements. In general, the tonus of the muscle wall of the intestine appeared to remain unchanged even with strong stimuli, although in one instance spasticity was observed. Similarly, the tonicity of the blood vessels in the gut wall usually seemed un-

affected except when spasticity of the intestinal musculature itself induced blanching. However, in those animals in which transitory engorgement or constriction of the vessels had been elicited by weak stimuli, the use of stronger currents led to a corresponding increase in the vasomotor responses.

*Effects of the injection of strychnine into the diencephalon.** When 0.05 cc. of a solution containing 0.07 to 0.08 mg. per kilogram of strychnine sulphate was injected into either side of the tuber cinereum the pendular movements of the intestinal loops were sometimes slightly increased, but the rhythmic segmentation and peristalsis, the tonicity of the muscular wall and the state of the blood vessels remained unaffected. However, administration of larger amounts of strychnine (up to 0.20 mg. per kilogram) was always followed by abolition of motility and increased tonicity and blanching of the gut whether or not other sympathetic responses were concurrently elicited. A second injection of strychnine from 30 to 45 mins. after the effects of the first had worn off produced reactions in the gut similar to those induced by the initial injection.

When the toxic effects of large or repeated injections of strychnine began to appear (gradually falling blood pressure, disturbed respirations and convulsions), the intestine usually became motionless, spastic and cyanotic. In several animals, just before fatal respiratory paralysis supervened, the gut showed a vigorous burst of peristaltic and pendular movements despite the presence of marked spasticity and cyanosis.

Changes in threshold. Electrical stimulation of the right side of the tuber cinereum following the local injection of 0.07 to 0.08 mg. per kilogram of strychnine sulphate revealed inconsistently lowered thresholds for the intestinal motor responses. Similarly, depressant effects on the gut associated with emotional mimetic responses could usually be elicited with currents weaker than those necessary before the injection of the strychnine salt. When stronger stimuli were applied to the tuber, especially after large or repeated injections of strychnine, transient convulsions were usually induced and always foreshadowed ultimate respiratory failure. During this period the gut gradually became motionless, spastic and cyanotic, while the thresholds mounted rapidly until practically all responses to hypothalamic stimulation were abolished a few minutes before death.

Recovery preparations

A total of 23 fluoroscopic observations were made upon the 6 animals in this series. In 15 of these the hypothalamus was stimulated with currents which were too weak (0.05 to 2.0 volts AC) to cause overt emotional mimetic responses; that is, reactions other than those in the alimentary tract consisted

* *Control Injections:* As shown in previous experiments (see reference in first footnote p. 350), the intradiencephalic injection of normal saline or Ringer's solution in amounts up to 0.2 cc. produces no observable effects and exerts no influence on the thresholds of electrical excitability if the injections are made at a rate of less than 0.1 cc. per min. When small amounts of India ink are added to the solution, the ink granules appear in minute tracts about the needle and, to a variable extent, in the third ventricle.

only in a slight restlessness and some increase in the rate of respiration. Nevertheless, in 11 of these 15 experiments segmentation and peristalsis in the small intestine were either initiated or definitely augmented and in one of the animals marked pendular movements were also induced. The intestinal responses appeared in from 5 to 15 secs. after the beginning of the stimulus and persisted for as much as 30 secs. after its cessation. In 2 of the animals in this series and in a number of others reported in previous communications,† retching and vomiting were observed during stimulation of the hypothalamus with weak or moderate currents. Of the other 4 experiments in which weak currents were used, 2 showed no change in the existing motility of the gut and in 2 the activity was found to be diminished. For the most part the entire small intestine appeared to respond as a unit.

In the remaining 8 experiments, strengths of current sufficient to induce widespread vegetative and emotional mimetic responses (2.0 to 6.0 volts AC) were employed. The general reactions then consisted in dilatation of the pupils, piloerection, extrusion of the claws, marked restlessness, hissing, growling and finally, fairly well directed clawing, fighting or running movements.* During these responses and from 5 to 60 secs. thereafter the motility of the small intestine was diminished or abolished; further, the degree and persistence of the intestinal inhibition appeared to correspond directly with the vigor of the emotional mimetic effects produced by the hypothalamic stimulation. Similarly, in 2 animals which became markedly disturbed by accidental shocks from static charges on the fluoroscopic apparatus, the intestinal tract, as viewed fluoroscopically, became markedly atonic. In these animals, moreover, hypothalamic stimulation with weak currents was without effect until they had become quiet and spontaneous intestinal motility had returned, at which time typical augmentation of activity was obtained.

Effect of strychnine in recovery preparations. Injections of from 0.07 to 0.08 mg. per kilogram of strychnine sulphate into the diencephalon caused little or no change in the rate of segmentation and peristalsis of the intestine if the other sympathetic effects of the injection were mild. However, when the vegetative and emotional mimetic effects were marked, intestinal motility was uniformly found to be depressed. Stimulation of the hypothalamus following its injection with strychnine in recovery preparations revealed fairly consistently diminished thresholds for both the enteromotor and general emotional mimetic responses.

Discussion

In 1932 Beattie[1] demonstrated that electrical stimulation of the tuber cinereum in an anesthetized cat gave rise to vagal impulses which induced increased peristalsis and secretion in the animal's stomach. Beattie also

† Masserman, J. H.: The effects of strychnine on the functions of the hypothalamus in emotional expression. *J. Pharmacol.* In press. Masserman, J. H.: The effects of pentamethylenetetrazol (metrazol) on the hypothalamus. *Arch. Neurol. Psychiat., Chicago.* In press.

* See references in first footnote p. 350.

anastomosed the central stump of one of the vagi with the peripheral end of the homolateral phrenic nerve and found that stimulation of the tuber 180 days after operation caused contraction of the diaphragm. Beattie and Sheehan[2] later reported that stimulation of the tuber cinereum raised the intragastric pressure independently of the peristaltic activity and that stimulation of the caudal portions of the hypothalamus diminished the intragastric pressure slightly and abolished gastric motility. Cushing[3] observed that marked hypervagotonic effects upon gastric motility followed injections of pituitrin and pilocarpine into the lateral ventricle in 3 of his patients, and regarded these reactions as evidence for a parasympathetic center in the interbrain. Finally, Kabat, Anson, Magoun and Ranson[4] fluoroscoped recovery preparations of cats and reported that inhibition of gastro-intestinal tonus and cessation of peristalsis occurred when structures in and about the hypothalamus were stimulated with currents sufficiently strong to induce marked emotional mimetic behavior and other evidences of widespread sympathetic discharge. These findings are in accord with our observations in experiments with these strengths of stimuli; however, we found in addition that weaker currents almost as uniformly increased intestinal motility, although the difference between motor and inhibitory effects was, in several of our experiments, as small as one volt.

Summary

The effects of electrical stimulation of the hypothalamus and of the injection of strychnine into the diencephalon upon the motility and blood supply of the small intestine were examined by direct inspection in cats anesthetized with ether and by fluoroscopy in recovery preparations. Observations in 14 animals led to the following conclusions:

1. Stimulation of the anterior portion of the hypothalamus with currents too weak to induce typical emotional mimetic responses in an anesthetized animal causes marked pendular movements of loops of small intestine and, less consistently, segmentation and peristalsis of the gut. In some animals these stimuli cause the small vessels in the external intestinal wall to constrict or dilate slightly, but more frequently no change in vasotonicity can be observed. In the recovery preparations segmentation and peristalsis are induced or augmented more consistently than are the pendular movements.

2. Enteromotor effects are also obtained when the dorsal portion of the supramammillary decussation and the mammillary bodies are stimulated.

3. Inhibition of intestinal motility is induced by the application of strong electrical stimuli anywhere in the hypothalamus and of weak stimuli in the suprachiasmic region or in the ventral portion of the supramammillary decussation. In stimulation of the hypothalamus the degree of intestinal inhibition corresponds to the intensity of the other autonomic and emotional mimetic responses elicited by the stimulus.

4. Injections of from 0.07 to 0.08 mg. per kilogram of strychnine sulphate into the diencephalon in cats causes either no change in intestinal activity or a slight accentuation in the intestinal movements. However, the injection

of larger amounts of strychnine into the diencephalon is consistently followed by spasticity, diminished motility and blanching of the small intestine.

5. Electrical stimulation of the hypothalamus after its injection with strychnine reveals inconsistently lowered thresholds for the diencephalic enteromotor reactions, the degree of intestinal inhibition in general corresponding to the degree of facilitation of the other vegetative and emotional mimetic responses of the animal to hypothalamic stimulation.

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ON THE RELATIONSHIP BETWEEN CHOLINE ESTERASE AND THE DEVELOPMENT OF BEHAVIOR IN AMPHIBIA

KARL ARDEN YOUNGSTROM
Department of Anatomy, Duke University School of Medicine, Durham, North Carolina

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Introduction

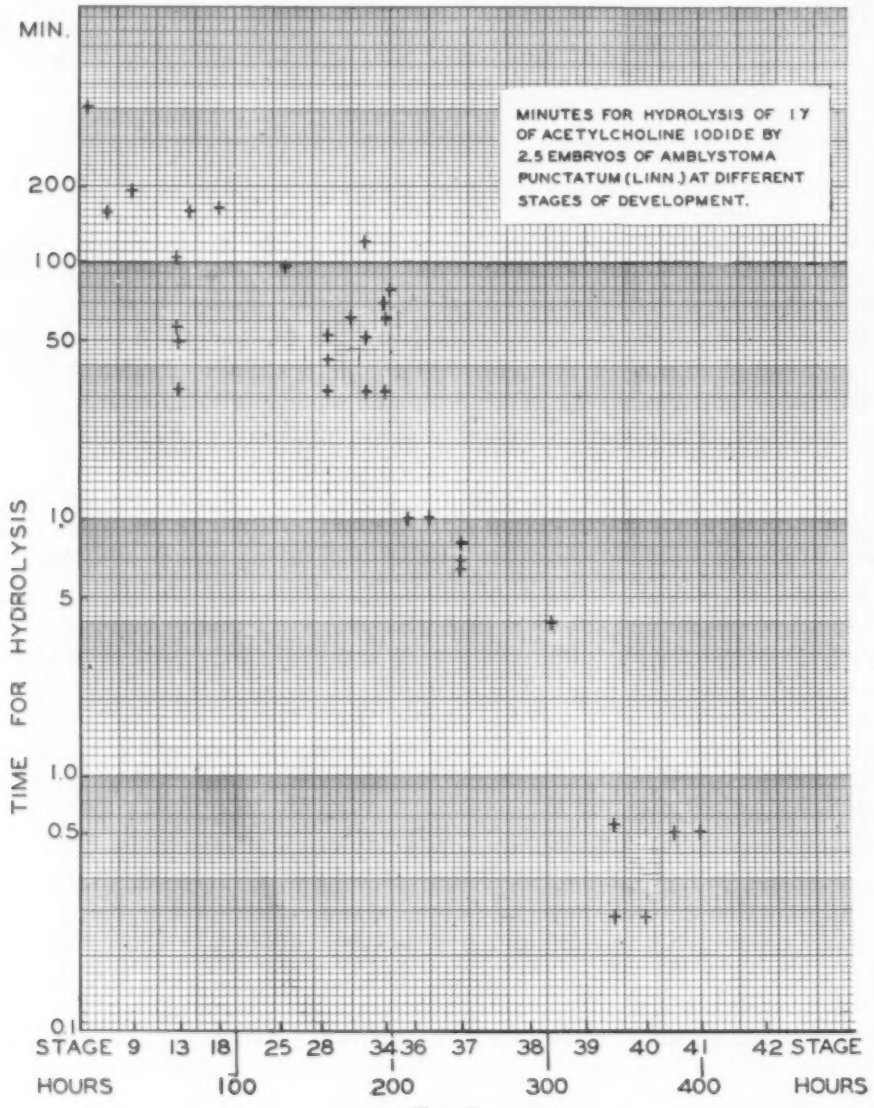
THE DESTRUCTION of acetylcholine by the enzyme choline esterase is thought to account for the short duration of the effect of a nerve stimulus (Dale, 1936). It has been shown that acetylcholine is liberated sometime after a motor nerve to striated muscle is stimulated (Dale, Feldberg and Vogt, 1936); and the amount of choline esterase present in the superior cervical ganglion is sufficient to accomplish the destruction of the acetylcholine liberated, presumably within the refractory period of that ganglion (Glick, 1938). The inactivation of choline esterase by eserine is well known (Gaddum, 1935). The behavior of amphibian embryos poisoned with eserine during the swimming stage is characterized by a gradual paralysis of the skeletal musculature, by a gradual loss of irritability to mechanical stimulation and by the development of contracture. A similar paralysis and contracture have been observed in amphibian embryos in the early swimming stage after they had been made to swim continuously for a few minutes by repeated mechanical stimulation. Therefore, it would seem that the slow relaxation of young amphibian embryos in the flexure, "U," and coil stages, and their quick fatigue through the early swimming stage* might be related to some developmental condition in the embryos affecting the relations between choline esterase and its substrate, acetylcholine.

This is somewhat different from the explanation offered by McCouch (Coghill, 1929, p. 14). He suggested three factors which might act to prolong the coil reflex in Amblystoma: (i) The "early stage of development of the muscle and neurones," (ii) opposition to the movement by the "tonic contraction of muscles on the side of the exteroceptive stimulus," (iii) "the resulting increased tension in the muscles of the convex side may set up proprioceptive stimuli which accentuate and prolong the coil reflex." The first factor pertains to the differentiation of the tissues, and is related to the object of the present study. The second factor might be related to the low esterase content of this stage. The third factor, being based on the idea that proprioceptive stimuli may initiate muscular activity, is contrary to the report by Kato (1934) that proprioceptive fibers when stimulated give no response. That this finding may

* Descriptions of these physiological stages are found in the publications of Coghill, 1929; Herrick, 1937; and Youngstrom, 1938.

hold also for the proprioceptive endings of the Rohon-Beard cells is, of course, open to question.

Assuming that acetylcholine is liberated by the nervous system of these embryos, its effect on the somites would be influenced by at least three fac-


MIN.
200
100
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10
5
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0.1
TIME FOR HYDROLYSIS
MINUTES FOR HYDROLYSIS OF 1% OF ACETYLCHOLINE IODIDE BY 2.5 EMBRYOS OF AMBLYSTOMA PUNCTATUM (LINN.) AT DIFFERENT STAGES OF DEVELOPMENT.
STAGE 9 13 18 25 28 34 36 37 38 39 40 41 42 STAGE
HOURS 100 200 300 400 HOURS

FIG. 1

tors: (i) The gradually decreasing concentration of salts in the embryo during the period of development (Schaper, 1902; Dempster, 1933; Youngstrom, 1938) might help to make the developing somites more sensitive to acetylcholine.* (ii) The avascular condition of the nervous and muscular tissues

* Clark (1927) has shown that a reduction of potassium in Ringer's solution increased the sensitivity of the heart to acetylcholine while an increase of potassium or calcium reduced this sensitivity.

until the swimming stage (Coghill and Moore, 1924) would allow the products of the choline esterase hydrolysis to accumulate locally. (iii) The amount of choline esterase present would influence the rate of destruction of the acetylcholine. If the amount of choline esterase were relatively small, acetylcholine might accumulate in the muscles. In this event one would expect

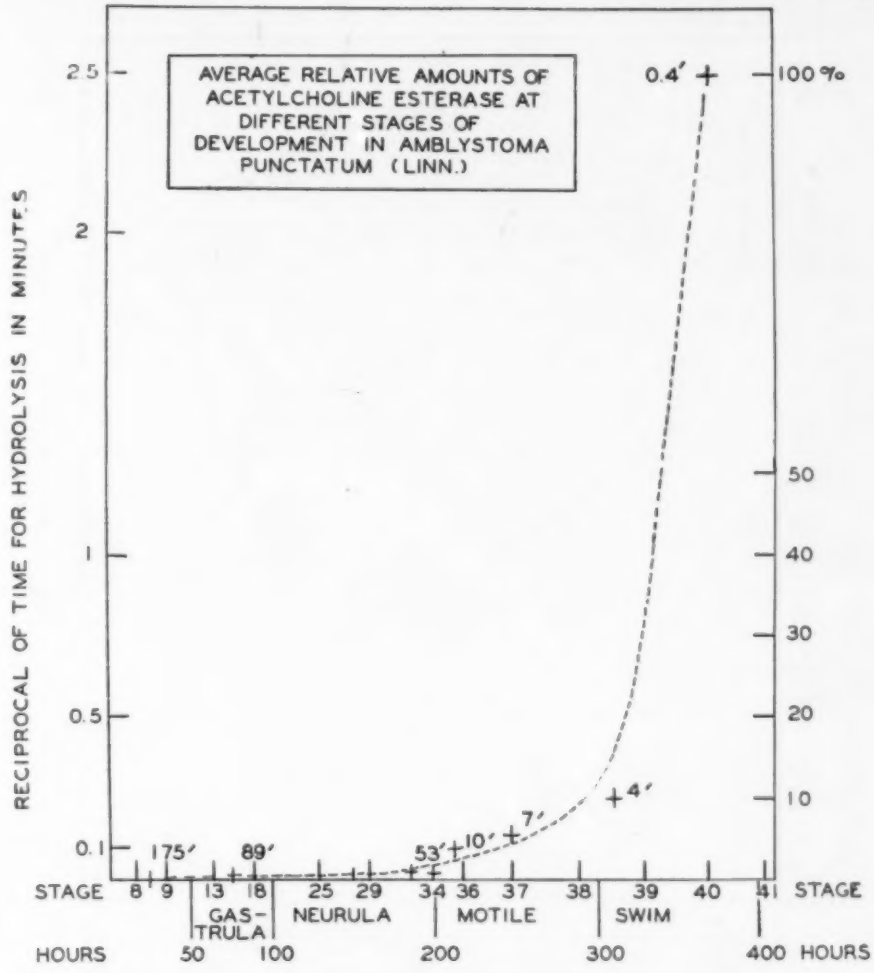

FIG. 2

from the work of Brown (1937) that the somites of both sides of the embryo would be in a state of partial tetanus. The developing behavior of these embryos is in harmony with this idea. To determine the amount of choline esterase present during the period of developing motility is the object of this study.

MATERIAL AND METHODS

Embryos of *Amblystoma punctatum*, *Bufo terrestris*, and *Rana sphenocephala* were used in these experiments. A definite number of embryos were selected according to their degree of morphological development*; and their type of reaction to mechanical stimuli.

* The *Amblystoma* embryos were staged according to Harrison's figures for the normal development of this form.

They were then ground in a mortar and made up to a standard volume with water and a limited amount of phosphate buffer pH 7.61. A definite amount of this suspension was added to a known amount of acetylcholine iodide solution, and samples of this mixture were tested at frequent intervals on guinea pig ileum after the method of Bernheim and Bernheim (1936). Failure of the gut to respond to the standardized test samples indicated the destruction of a definite amount of acetylcholine iodide. The preparations were sensitive to acetylcholine iodide diluted to 1 part in 7,500,000. This is a greater sensitivity

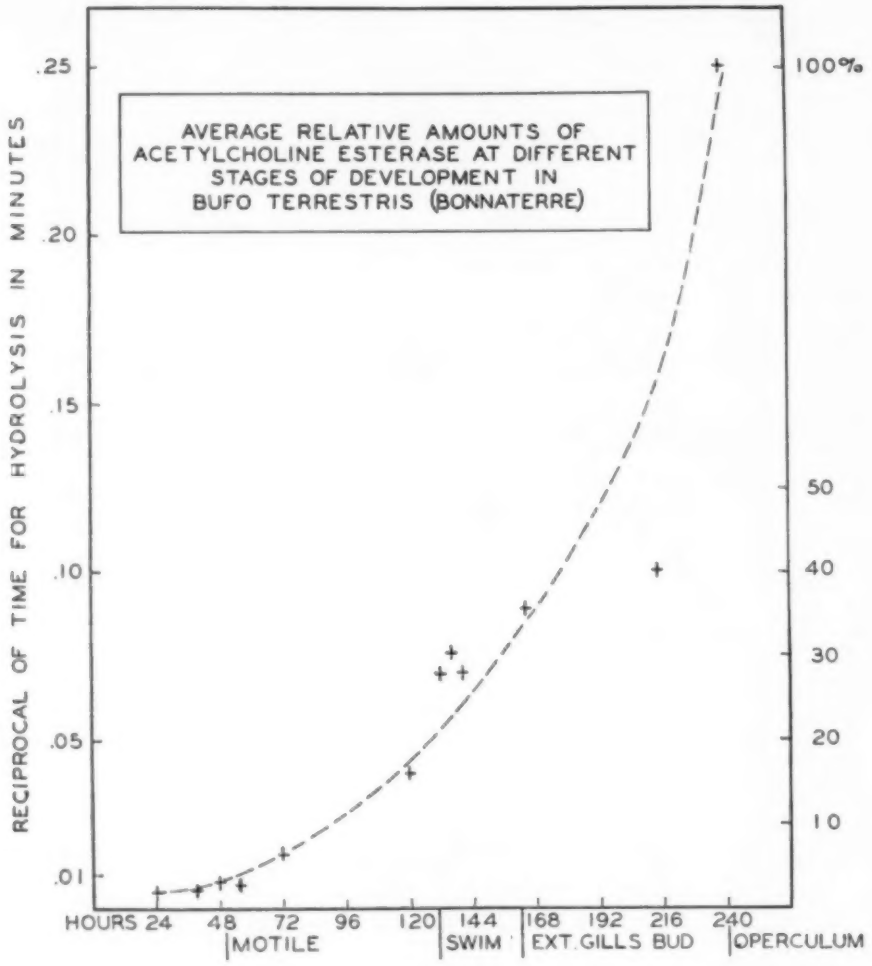

FIG. 3

than was ascribed to this method by the Bernheims, because the use of a smaller vessel made it possible to suspend the guinea pig ileum in only 15 cc. of fluid.

The total amount of enzyme present was found to be so small that no attempt was made to extract it. The effect on guinea pig ileum of the ground embryo suspension itself as well as that of the alkaline buffer, was controlled by using test samples which contained less than threshold amounts of these substances.

The temperature during the time the enzyme and substrate were allowed to react was held constant for each series. The determinations on *Amblystoma punctatum* were done at 37°C.; those on *Bufo terrestris* and *Rana sphenocephala*, were done at 25°C.

Results

The amount of choline esterase present at different stages of development in the three species studied is presented graphically in Figs. 1 to 4. Fig. 1 is plotted on semi-log paper to show the distribution of the data. Fig. 2 is constructed from the same data to show directly the relative amount of enzyme. In Fig. 1 each + sign represents one determination, while in Figs. 2, 3 and 4

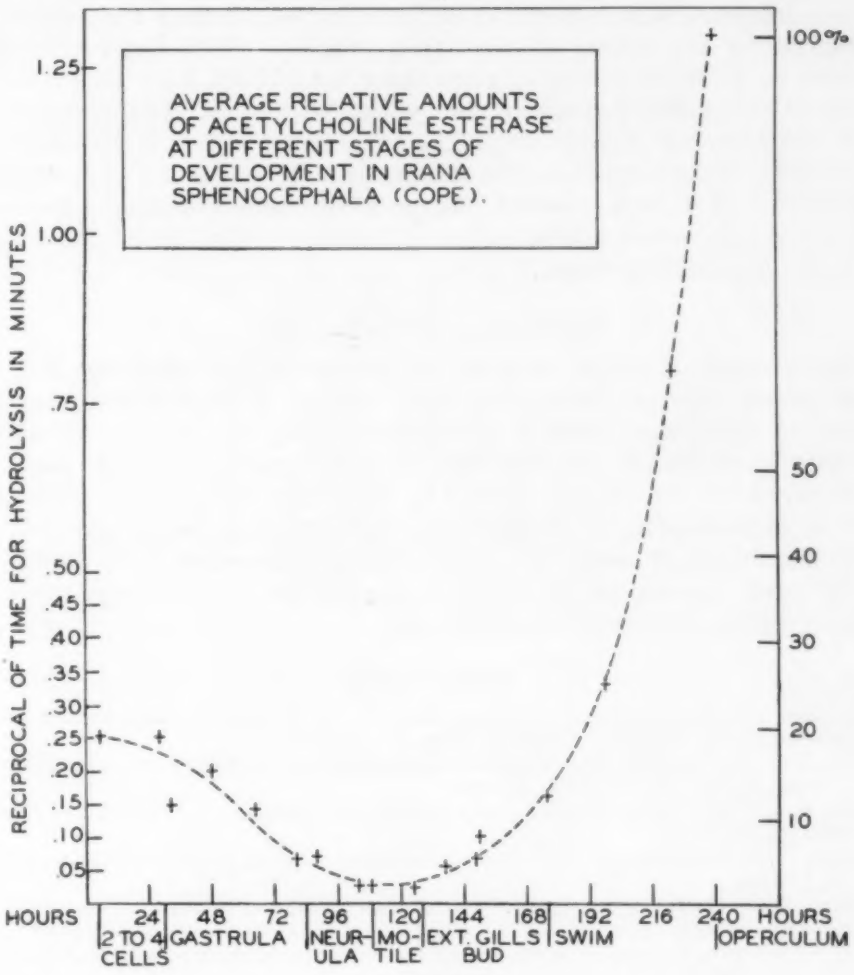

FIG. 4

each + represents the average of several determinations. The ordinate scale represents time in Fig. 1. In Figs. 2, 3 and 4 it represents the reciprocal of the times for hydrolysis of 1 gamma of acetylcholine iodide by 2.5 Amblystoma embryos, by 1.25 toad embryos and by 5 frog embryos, respectively. The percentage scale arbitrarily represents the highest value on each graph as 100 per cent.

The difference in the ordinate scale as observed in Figs. 2, 3 and 4 may

be explained largely on the basis of the difference in dry weight of the three species. The average dry weight of an individual embryo in the early swimming stage is 2.2 mg., 0.5 mg., and 1.3 mg. for *Amblystoma punctatum*, *Bufo terrestris* and *Rana sphenocephala*, respectively. The increase in the amount of the enzyme would be relatively greater if it were expressed in terms of dry weight instead of the number of embryos, because the dry weight is decreasing slightly during this phase of development. Although there is considerable species difference in the character of these curves, all show a significant increase during the period of developing motility. From the beginning of motility to the early swimming stage there is a 13 fold, 5 fold and 5 fold increase of the choline esterase in *Amblystoma punctatum*, *Bufo terrestris*, and *Rana sphenocephala*, respectively. The enzyme, moreover, is present before the nervous system appears. The amount is then very small in *Amblystoma punctatum* and in *Bufo terrestris*, but quite considerable in *Rana sphenocephala*. In the last named species it is as abundant in the 2 and 4 cell stage as in the early swimming stage.

Summary and Conclusions

The amount of choline esterase present during representative stages of development has been determined for 3 species of amphibian embryos. A significant increase occurred in all 3 species during the period of developing motility. These data do not bear directly on the explanation of the prolonged character of the coil reaction offered by McCouch, but should contribute to a better understanding of the slow relaxation and early fatigue of young amphibian embryos. It seems that a satisfactory explanation of developing behavior must consider neurohumoral factors of nerve physiology, as well as the developing patterns of neuroanatomy.

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SENSORIMOTOR CORTEX, NUCLEUS CAUDATUS AND THALAMUS OPTICUS*

J. G. DUSSER de BARENNE AND W. S. McCULLOCH
From the Laboratory of Neurophysiology, Yale University School of Medicine

(Received for publication, June 1, 1938)

INTRODUCTION

SEVERAL anatomists (Cajal,[1] Marinesco,[10] Minkowksi,[11] Kariya,[8] Hirasawa and Kariya[7]) have described corticostriatal neurons, originating in the sensorimotor cortex. Nevertheless the present tendency in neuroanatomy and neurology is to ignore these findings and to maintain that the cerebral cortex does not directly influence the activity of the striatum, an opinion understandable in the absence of physiological evidence of a directed functional relation from cortex to striatum.

In this paper† direct experimental evidence for such a functional relation is presented. It will be shown: (i) that two specific areas of the sensorimotor cortex, namely the areas L.4-s and A.4-s‡ influence the activity of one of the constituent portions of the striatum, *viz.*, the nucleus caudatus, (ii) that these areas L.4-s and A.4-s via this nucleus influence the activity of the thalamus, and (iii) that these areas via nucleus caudatus and thalamus influence the activity of two other areas, *viz.*, the leg-and arm-portions of area 4 (L.4 and A.4) of the sensorimotor cortex. In other words, in this paper will be demonstrated by physiological methods the existence and operation of the following one-way system:

Areas L.4-s and A.4-s→nucleus caudatus··→thalamus opticus→areas L.4 and A.4

This has been done by combining recording of electrical activity, local strychninization and operative lesions of the nervous structures involved. The connection between the caudate nucleus and thalamus has been indicated by a dotted arrow, because the course of the neurons establishing this connection is as yet uncertain (see discussion, p. 376).

METHODS

All experiments were performed on monkeys (*Macaca mulatta*) fully anesthetized with Dial§ (0.45 cc. per kilogram bodyweight, half of the dose given intraperitoneally, half intramuscularly). In some experiments curarization was used.

In these experiments the method of local strychninization was combined, as in previous investigations[2,3] with that of recording the electrical activity of various levels of the brain. The local strychninizations of the caudate nucleus were performed by injecting minute quantities of a 3 per cent strychnine solution (0.3–1.0 cmm. = 10–30γ of strychnine) by

* The expenses of this investigation were defrayed by a grant from the Fluid Research Funds of Yale University, School of Medicine.

† A preliminary report of this investigation was presented before the annual meeting of the American Neurological Association at Atlantic City on May 3, 1938.

‡ For the designation of the various cortical areas see Dusser de Barenne and McCulloch.[2]

§ The Dial was kindly put at our disposal by the Ciba Company.

means of the micro-injection method developed by Dusser de Barenne and Sager.[4,5] The electrical activity from the various portions of the sensorimotor cortex (electrocorticogram: ECG) was recorded simultaneously with bipolar Ag-$AgCl_2$ electrodes through AC-amplifiers and a Westinghouse four-element oscillograph; the electrograms from the subcortical structures, the caudate nucleus and the various thalamic nuclei, were taken with concentric needle-electrodes,[3] in which the inner insulated electrode protruded 1.5 mm. beyond the outer one, the hypodermic needle proper. The animals and the electrodes were placed on a table in a large Faraday-cage, so that the recordings of the electrical activity were undisturbed by extraneous electrical fields.

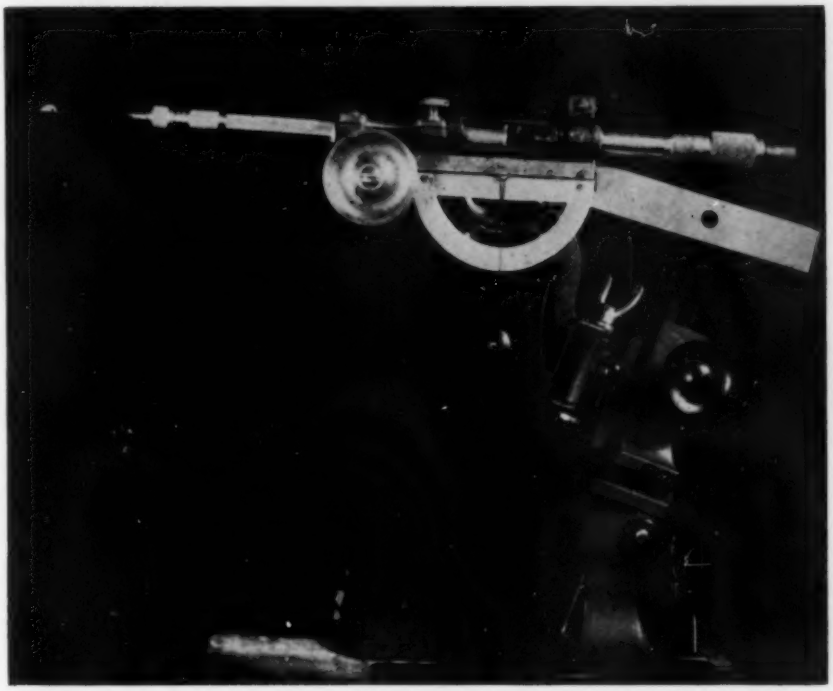

FIG. 1. "Knife," a little piece of thin flat steel sharpened at the edge, on needle-holder and stand for placing small lesions in subcortical structures. As a holder for the needle with the knife serves a pinvise, which can be rotated around its length-axis on a closely fitting pin mounted rigidly in the micro-injection apparatus. Thus a small lesion can be made in the particular subcortical structure. The needle is withdrawn in the same vertical position in which it was introduced; thus the smallest possible "track" outside the desired subcortical structure is obtained.

In a number of the experiments localized lesions were made in various subcortical structures, *viz.*, the optic thalamus, the caudate nucleus and other portions of the striatum. The apparatus was a little "knife" soldered to the end of an ordinary sewingneedle and mounted on a needle-holder, instead of the tuberculin-syringe, in a microinjection apparatus of Dusser de Barenne and Sager (see Fig. 1). This "knife" was introduced into the desired subcortical structure in a vertical plane, then the needle-holder was turned 360° around its length-axis; thus the knife produced a sharply localized, olive-shaped lesion, the shape and size of which is determined by the shape and size of the "knife." The length of such a lesion can be increased by screwing the "knife" back by the micrometer-screw of the apparatus over a few millimeters and then repeating the rotation around the length-axis of the needle. Finally the "knife" was withdrawn from the brain by screwing it back in its original position in the vertical plane.

Results

As shown previously[2] the local strychninization of area A.4-s or L.4-s results in a temporary suppression of the electrical activity of the areas A.4 and L.4. It was stated there that this suppression does not depend upon interareal connections, but occurs via one or more subcortical structures. This statement was based upon the following two groups of experiments.

A. (i). An incision between area A.4-s and area A.4, 10 to 12 mm. deep, does not prevent this suppression (see Fig. 2).

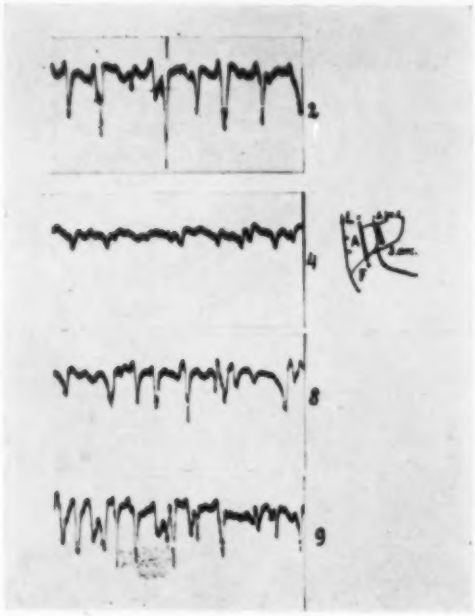

Fig. 2. October 18, 1937. Macaque. Dial-narcosis. ECG of area A.4 (:) before (record 2) and after (records 4, 8 and 9) local strychninization of area A.4-s. Before the records were taken a deep cut ($\frac{x}{x}$), 9½ mm. deep, was made between A.4 and A.4-s. Record 4 taken two minutes, record 8 nine minutes and record 9 thirteen minutes after the local strychninization of A.4-s. Note suppression in ECG of record 4 with gradual return to normal in records 8 and 9. Diagram: L, A, F = leg- arm- and face subdivisions of precentral sensorimotor cortex.: = position of electrodes on A.4. S. pr. S = Sulcus precentralis superior, S. arc. = S. arcuatus.

(ii). The undercutting of area A.4-s does prevent the suppression (see Fig. 3).

These two experiments prove that this suppression involves connections from area 4-s to some subcortical structure. The following experimental evidence points to the *nucleus caudatus*.

B. (i). The nucleus caudatus is "fired" by local strychninization of area 4-s, either L.4-s or A.4-s (see Fig. 4).

(ii). The nucleus caudatus is not "fired" by local strychninization of areas L.4, A.4, L.6a or A.6a (see Fig. 5). The site of strych-

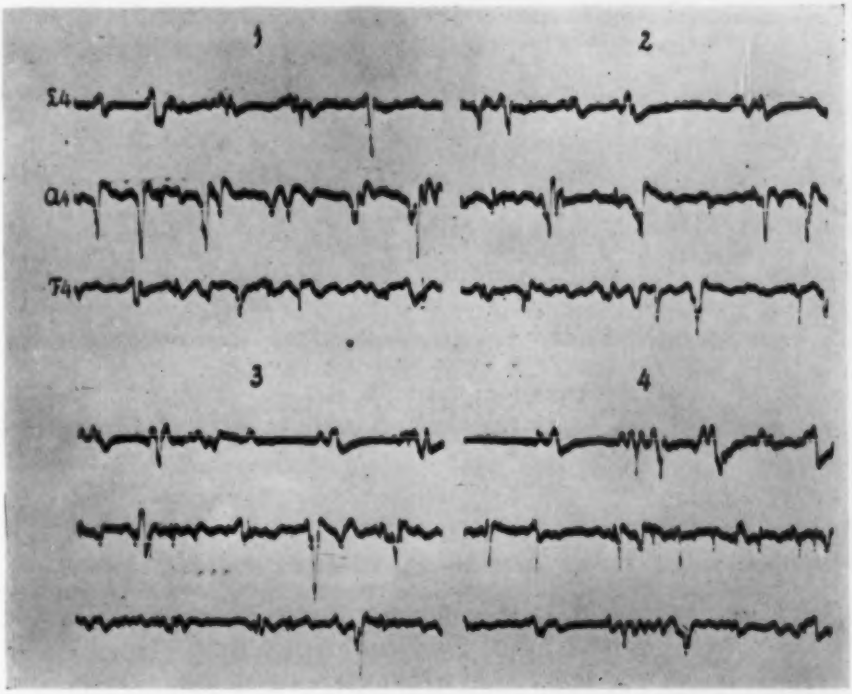

FIG. 3. October 20, 1937. Macaque. Dial-narcosis. ECGs from L.4, A.4 and F.4. All records taken after undercutting of A.4-s and L.4-s. Record 1 taken before local strychninization of A.4-s, records 2, 3 and 4 after this strychninization. Note absence of suppression in ECGs of A.4 and L.4.

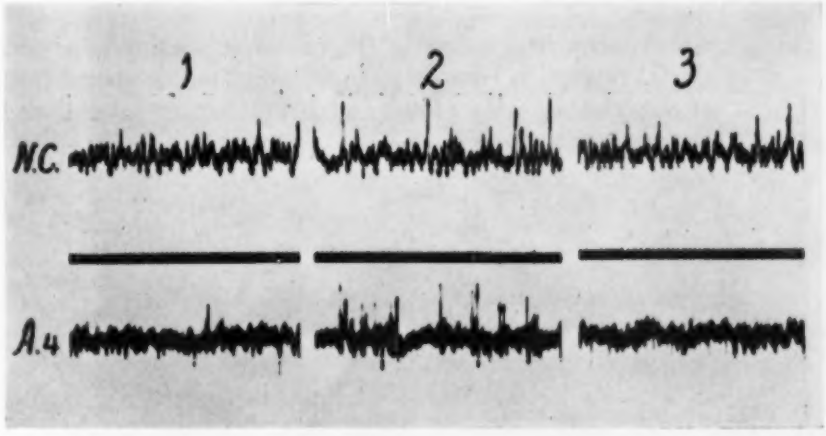

FIG. 4. February 14, 1938. Macaque. Dial-narcosis. Local strychninization of A.4-s resulting in strychnine-spikes in electrogram of nucleus caudatus. Record 1 before, record 2 five minutes after this strychninization, record 3 fifteen minutes later. The spiking in the ECG of A.4 (record 2) is due to the fact that the strychninization slightly encroached upon A.4.

ninization in the caudate nucleus in the particular experiment from which Figs. 4 and 5 are taken is shown in Fig. 6.

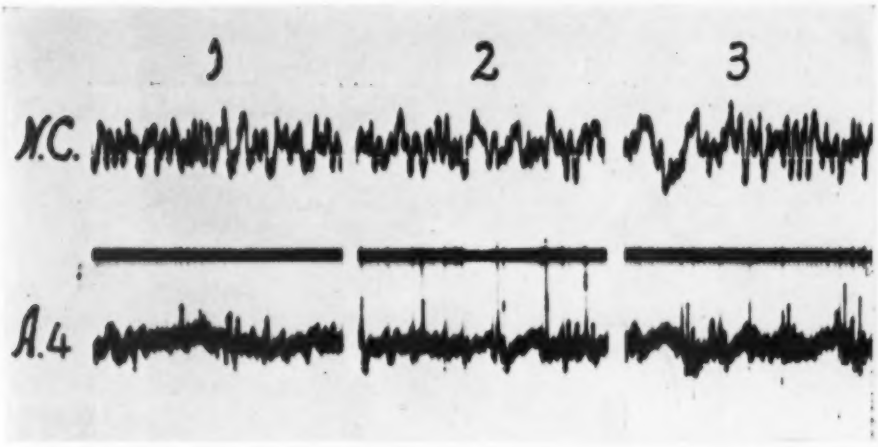

FIG. 5. Same animal as of Fig. 4. Record 1 electrograms of nucleus caudatus and A.4 before strychninization. Record 2 same after local strychninization of A.4: spiking in ECG of A.4, not in electrogram of N. C. Record 3 same after local strychninization of A.6a: spiking in ECG of A.4, no "firing" of nucleus caudatus.

The interpretation of these findings consistent with the conclusions from previous observations[2] is that the strychnine applied to area 4-s has acted upon perikarya of neurons with axons or axonal collaterals ending in and thus "firing" the caudate nucleus, and that of the areas mentioned above area 4-s only is directly connected with the caudate nucleus.

Further evidence implicating the caudate nucleus is found in the following groups of experiments.

C. (i). An experimental lesion in the occipital portion of the caput nuclei caudati is immediately followed by a marked increase of electrical activity of A.4 and L.4 persisting for half an hour to two hours (see Fig. 7b).

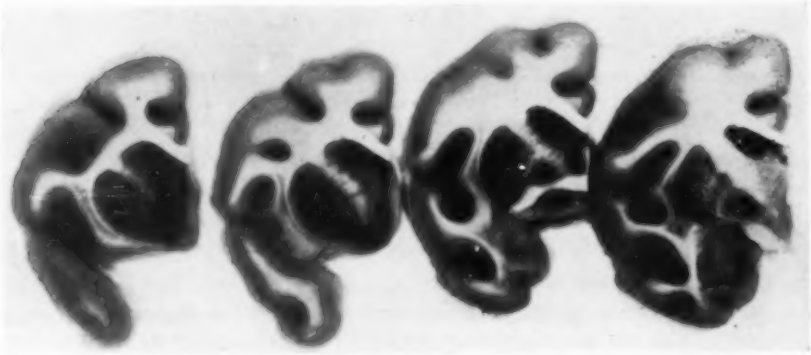

FIG. 6. Fig. 6 shows track of concentric needle-electrodes in nucleus caudatus of experiment of Figs. 4 and 5.

(ii). Subsequently, local strychninization of A.4-s or L.4-s fails to suppress the activity of A.4 and L.4 (Compare Fig. 7a (before) and 7c (after lesion in nucl. caud.))

The lesion made in the nucleus caudatus, which gave rise to the "release" of area A.4 pictured in Fig. 7b and prevented the suppression of area A.4 recorded in Fig. 7a and 7c, is shown in Fig. 8.

(iii). Local strychninization of the caudate nucleus results in a typical temporary suppression in areas A.4 and L.4, similar to that appearing after local strychninization of area A.4-s or area L.4-s (see Fig. 9). Comparing the ECG of A.4 in Fig. 9 (1) with that in Fig. 9 (3), it will be seen that the activity in the latter is definitely enhanced. This is a consistent finding, to be expected inasmuch as the introduction of a needle into the caudate nucleus inevitably produces a lesion. Apparently the suppression of the activity of area A.4 due to the hyperactivity of the locally strychninized caudate nucleus is sufficient to overshadow temporarily the "release" of this area by such a small destructive lesion. The site of strychninization in the caudate nucleus in the particular experiment from which Fig. 9 is taken is given in Fig. 10.

One of the few points upon which neuroanatomists unanimously agree is that in the caudate nucleus arise no corticopetal neurons, *i.e.*, they all deny the existence of caudatocortical axons, a conclusion substantiated by our repeated failures to find "firing" of any portion of the sensorimotor cortex by local strychninization of the caudate nucleus.

The experiments presented here show conclusively that the caudate nucleus affects the activity of areas A.4 and L.4. There must be, therefore, some indirect connection between this nucleus and these areas of the sensorimotor cortex. *This requires a subcortical structure which 1. is affected by the nucleus caudatus and 2. itself, in turn, affects the activity of A.4 and L.4 of the sensorimotor cortex.* All physiological and anatomical evidence points to the *optic thalamus.*

D. (i). Therefore, in several experiments the electrical activity of some of the arm- and leg-nuclei of the thalamus,[3] *i.e.*, the electrothalamograms (ETG) of these nuclei, were recorded simultaneously with the ECGs of areas A.4 and L.4, before and after local strychninization of the caudate nucleus. It was found that such strychninization temporarily suppresses the activity of the thalamus as well as that of areas A.4 and L.4 (see Fig. 11). In Fig. 12 is shown the position of the thalamic electrodes and the site of strychninization in the caudate nucleus in the particular experiment of Fig. 11. Thus the thalamus fulfils the first requirement mentioned above.

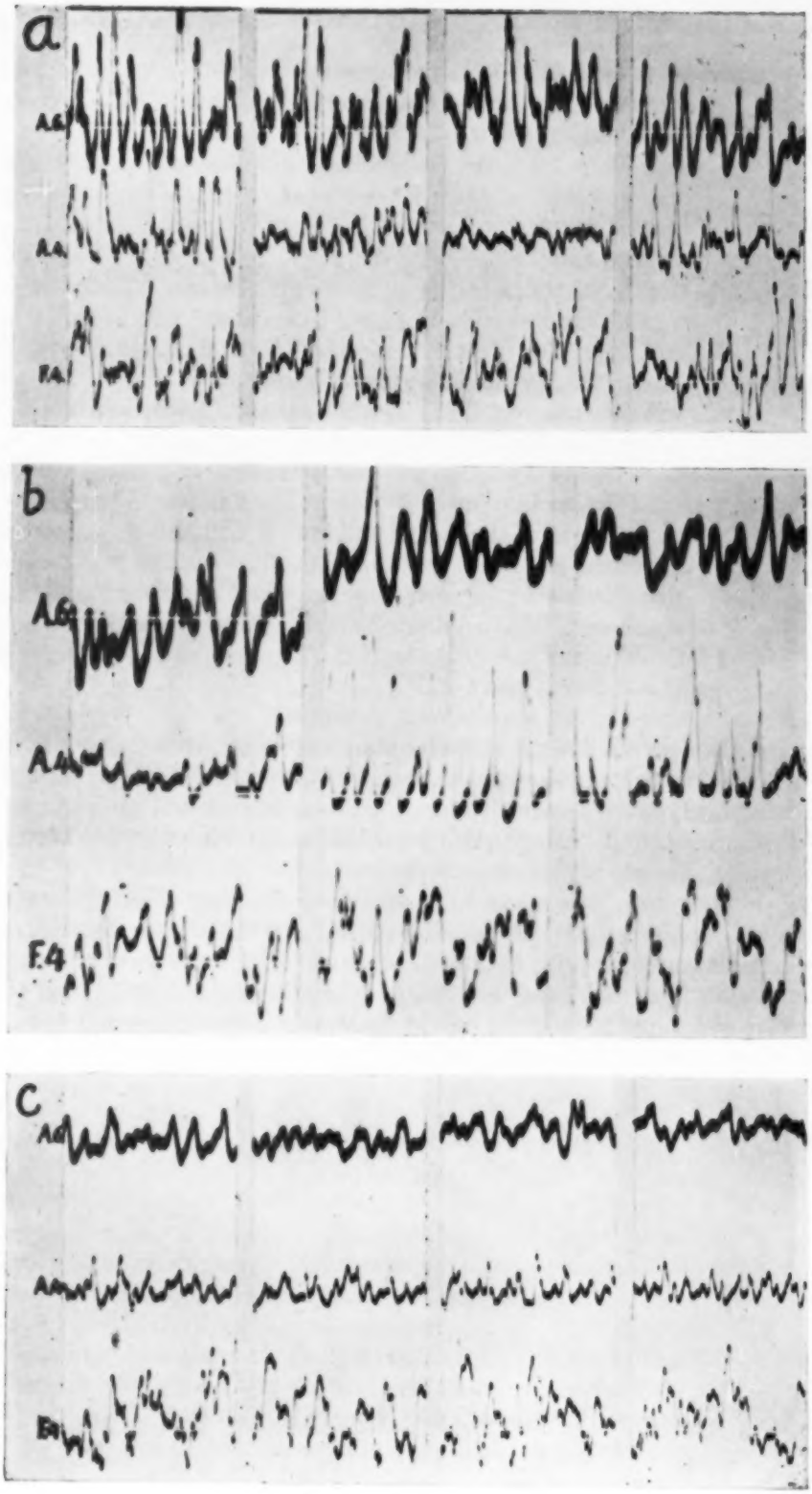

FIG. 7. (*For legend see opposite page.*)

(ii). With respect to the second requirement it has been stated in a previous paper[3] that strychninization of the thalamus results in "firing" of the sensorimotor cortex. Experiments of this kind show that, as one would expect, the thalamus affects the

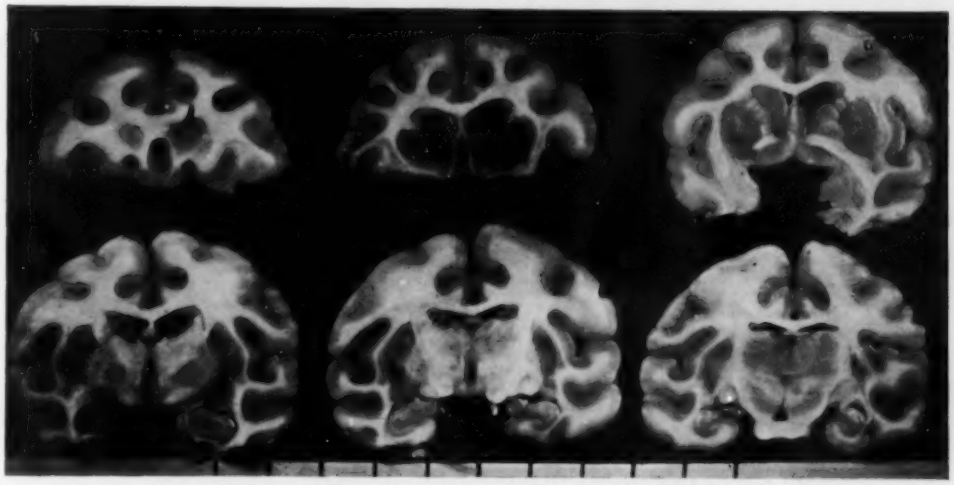

FIG. 8. This figure shows lesion of nucleus caudatus in experiment of Fig. 7.

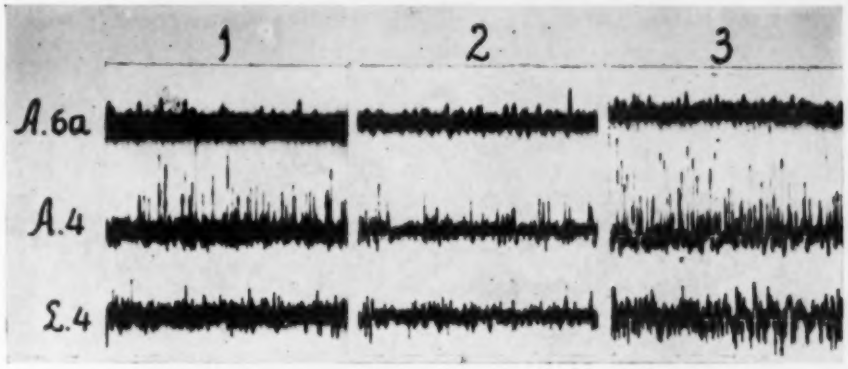

FIG. 9. February 10, 1938. Macaque. Dial-narcosis. Simultaneous ECGs of A.6a, A.4 and L.4. Typical temporary suppression of A.4 and L.4 in record 2 upon local strychninization of caudate nucleus, followed by "release" (due to lesion of caudate nucleus by injection-needle) in record 3. No essential change in ECG of A.6a.

activity of the cortex, but not that cortical activity depends upon thalamic activity. However, this can be shown by undercutting the sensorimotor cortex, thus destroying thalamocor-

FIG. 7. Macaque. Dial narcosis. Simultaneous ECGs of A.6, A.4, F.4. In Fig. *a* typical temporary suppression of A.4 upon local strychninization of A.4-s. In Fig. *b* "release" of A.4 after acute lesion in nucleus caudatus; record 1 of *b* before lesion. In Fig. *c* absence of suppression (after "release" has subsided several hours after lesion) upon local strychninization of A.4-s.

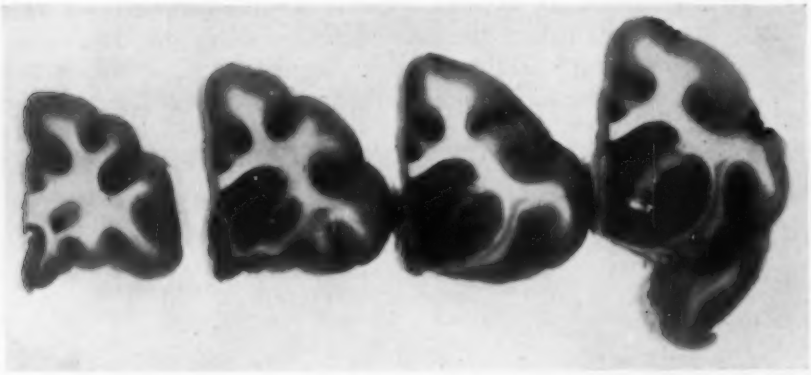

FIG. 10. Site of strychninization in caudate nucleus in experiment of Fig. 9.

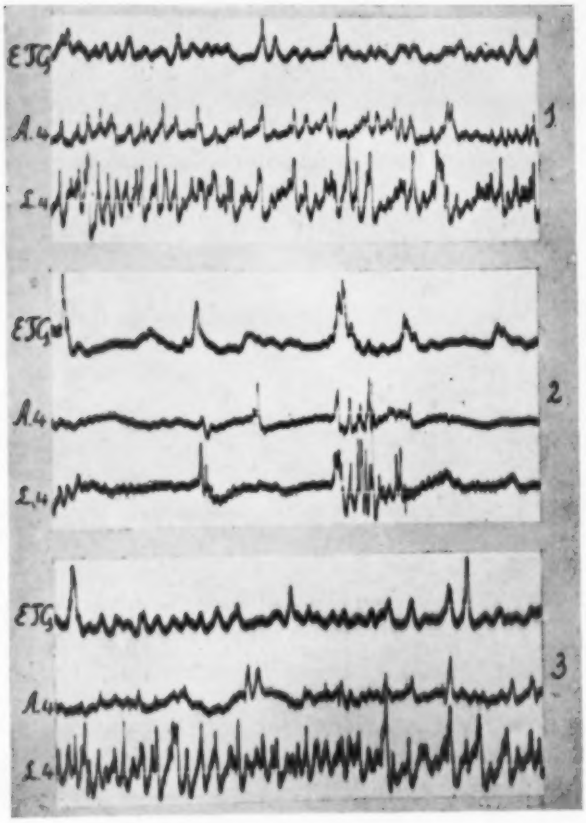

FIG. 11. Macaque. Dial-narcosis. ETG of a leg-nucleus of the thalamus and ECG of A.4 and L.4. Record 1 "normal"; in record 2, after local strychninization of caudate nucleus, suppression in ETG and ECGs. In record 3 return to "normal" of all electrograms.

tical connections. The simultaneous severance of the corticothalamic neurons is obviously of no importance here. In the acute experiment such an undercut cortex is "silent," *i.e.*, its electrical activity is abolished, though its threshold for cortical after-discharge to electrical stimulation, if altered at all, is slightly lowered. In the chronic experiment, even with undercutting of a portion of the sensorimotor cortex only, for

FIG. 12. This figure shows the position of the concentric needle-electrodes in nucleus *lb*iii (leg-nucleus) of the thalamus of the right hemisphere and the site of strychninization in the right caudate nucleus in experiment of Fig. 11. The needle-electrodes were introduced into the right thalamus through the left hemisphere so as not to damage the right corticothalamic and thalamocortical connections.

instance of the precentral arm-area, though the electrical activity has returned to some extent, the ECG, even after a survival period of 2.5 years, is highly abnormal. *These observations prove that the ECG normally depends directly on thalamic impulses impinging upon the cortex.*

The same can be shown by acute experimental lesions in the sensory nuclei of the thalamus. These also result in a marked diminution of the electrical activity in the corresponding subdivisions of the sensorimotor cortex. Yet, even the residual cortical activity of areas A.4 and L.4 depending upon the remnants of the sensory nuclei of the thalamus still shows a trace of suppression upon local strychninization of the caudate nucleus (see Figs. 13 and 14).

Taken together, these results show that the thalamus fulfills both of the above mentioned requirements for a subcortical structure linking the caudate nucleus with areas A.4 and L.4 of the sensorimotor cortex.

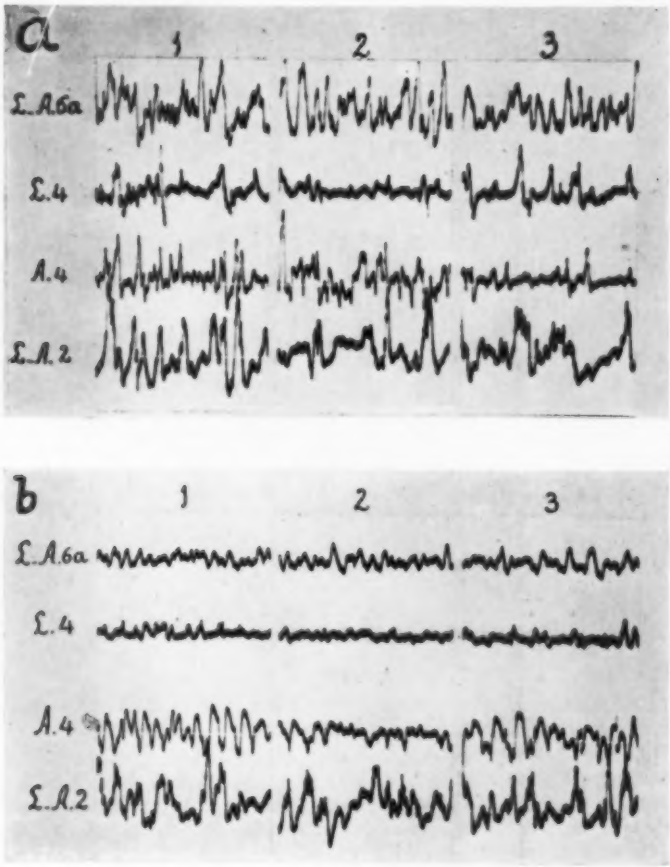

FIG. 13. March 18, 1938. Macaque. Dial-narcosis. Fig. 13 *a* shows ECGs of various cortical areas before and after local strychninization of A.4-s. Note suppression in ECG of L.4 in 2 and in ECG of A.4 in 3. The records of Fig. 13 *b* were taken almost two hours after a lesion of the leg-nuclei of the thalamus. Record 1 before, records 2 and 3 after local strychninization of A.4-s. Note the typical suppression in ECG of A.4 in record 2 with return to normal in record 3. Note also that even the reduced activity of L.4, due to the lesion of the leg nuclei, is temporarily somewhat suppressed (record 2).

DISCUSSION

The experiments reported in this paper are concerned only with the precentral portions of the arm- and leg- subdivisions of the sensorimotor cortex, the corresponding sensory nuclei of the thalamus and the posterior portion of the caput and the anterior portion of the cauda of the nucleus caudatus. Neither strychninization nor lesion of these structures has appreciably altered the electrical activity of area F.4. These statements constitute important re-

strictions because it has been found that the functional organization in the precentral face-subdivision of the sensorimotor cortex is so different from that in the precentral arm- and leg-subdivisions that the subject must be dealt with in a separate paper.

As mentioned previously[2] our areas A.4-s and L.4-s are identical with that portion of the "strip" of Marion Hines[6] which lies on the outer surface of the arm- and leg-subdivisions of the sensorimotor cortex. The striking analogy of her finding, namely abolition of existing motor activity on electrical stimulation of the "strip," with our suppression, the abolition of an existing elec-

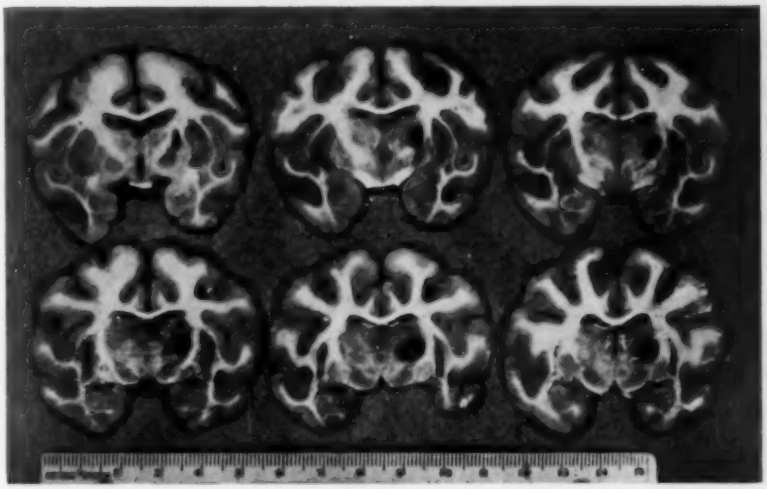

FIG. 14. Lesion of some of the leg-nuclei of the thalamus in experiment of Fig. 13. There is a slight haemorrhage also in nucleus va (arm nucleus) in middle picture of bottom row. In the first picture the slit made by the introduction of the "knife" in the vertical position is seen; the oval lesions in the subsequent pictures are made by the rotation of the "knife" around its length-axis.

trical activity of areas A.4 and L.4 upon local strychninization of the "strip" (A.4-s and L.4-s), has been mentioned there too. Now another analogy has become apparent. We have not indeed destroyed the "strip," which operation in the hands of Marion Hines resulted in spasticity for some days, but we have destroyed a large portion of the nucleus caudatus (shown here to be a necessary link in the pathway from areas 4-s to the thalamus and so to areas A.4 and L.4 of the cortex), which resulted in a release of these areas for a matter of hours. Marion Hines has not shown what pathways emanating from her strip are involved in the production of the spasticity. Therefore, one cannot without more ado identify the subcortical structures involved in the production of this spasticity with those responsible for the "release" of areas A.4 and L.4. If these structures are significantly different, the durations of the disturbances might be different for that reason alone. Apart from this, our lesions in the caudate nucleus were far from complete destructions and the duration of our release depended upon the size of the lesion. Just so the

duration of spasticity varied with the extent of Hines' lesions. Finally it should be pointed out that our animals were fully anesthetized throughout the experiment, whereas Hines' animals were not under narcosis. These latter considerations indicate that the discrepancy in duration of the two phenomena is not a serious objection against the stated analogy. The fundamental difference is of course that Marion Hines investigated disturbances *descending* to striped muscle, whereas our experiments upon suppression of areas A.4 and L.4 dealt with disturbances affecting thalamocortical activity, *i.e., ascending* to the cerebral cortex.

In the introduction the linkage between the caudate nucleus and the thalamus was represented by a dotted arrow to indicate that its path is as yet undetermined. Neuroanatomy has not solved this problem. A few authors have described direct short caudatothalamic neurons; others have described longer caudatothalamic neurons running through the laminae medullares of putamen and globus pallidus, and still others—in fact the majority of neuroanatomists—deny the existence of both of these direct systems and acknowledge only indirect connections between the caudate nucleus and thalamus with a synaptic relay in the pallidum (see the synopsis by Kodama[9]). In this respect it is of interest that, although large lesions in the putamen do not cause "release" or prevent suppression of areas A.4 and L.4, one experiment in which such a lesion was extended into the pallidum did prevent suppression without causing release. By no such experiment can one distinguish between long direct caudatothalamic neurons and systems relayed in the pallidum. Yet this experiment does suggest that somehow impulses necessary for suppression pass through this region; it does not preclude the existence of or the necessity of activity in short direct caudatothalamic neurons.

That large lesions in the putamen neither cause release nor prevent suppression of areas A.4 and L.4 is entirely in harmony with the absence of any strychnine-spikes in the electrogram of the putamen upon local strychninization of areas A.4-s and L.4-s. These findings suffice to show that in spite of the anatomical homogeneity of the nucleus caudatus with the putamen, the latter is not a part of the system discussed in this paper.

From the observations reported here it is clear that the caudate nucleus "*brakes*" the activity of the thalamus and, via this structure, that of the areas A.4 and L.4 of the sensorimotor cortex. This is evidenced by the findings that a lesion in the caudate nucleus temporarily releases the activity of these cortical areas and that hyperactivity of this nucleus, induced by its local strychninization or by that of either area A.4-s or L.4-s of the sensorimotor cortex, suppresses the activity of areas A.4 and L.4 of this region of the cortex.

The experiments reported, therefore, constitute a demonstration *by physiological means* that the striatum, more particularly the caudate nucleus, does not function independently of the cerebral cortex. On the contrary; it has been shown here: (i) that specific areas (A-4.s and L.4-s) of the sensorimotor cortex directly influence, excite, or activate, the caudate nucleus, (ii) that the activity of this subcortical structure influences, or "brakes," albeit

indirectly via the optic thalamus, the activity of other equally specific areas (A.4 and L.4) of the same sensorimotor cortex.

Summary

1. The suppression of the electrical activity of A.4 and L.4 by local strychninization of A.4-s or L.4-s involves subcortical structures, namely, the nucleus caudatus and the thalamus opticus.

2. The nucleus caudatus is "fired" by local strychninization of A.4-s or L.4-s, but not by that of A.4, L.4, A.6a or L.6a.

3. A lesion in the nucleus caudatus temporarily "releases" A.4 and L.4.

4. Strychninization of the nucleus caudatus produces a typical suppression of the electrical activity of thalamus and of A.4 and L.4.

5. The normal electrical activity of the sensorimotor cortex depends upon the influx of thalamocortical impulses.

6. The putamen is not involved in this system.

7. The pathway from nucleus caudatus to thalamus is as yet undetermined.

8. The functional one-way system described in this paper is constituted as follows:

A.4-s and L.4-s → nucleus caudatus · · › thalamus opticus → A.4 and L.4.

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REFLEX DISCHARGE FROM THE SPINAL CORD OVER THE DORSAL ROOTS

JAN F. TOENNIES

From the Laboratories of The Rockefeller Institute for Medical Research, New York

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INTRODUCTION

THE EXPERIMENTS described in this paper started from an observation made on the saphenous nerve of the cat. In order to send controlled volleys of impulses toward the spinal cord, the usual stimulating electrodes had been supplemented with lead electrodes, so that the content of fibers active in the nerve could be ascertained. It was observed that, in addition to the potentials arising directly from the stimulating electrodes, there appeared a large group of potentials resembling closely the reflex discharge that is seen in a mixed nerve in sequence to an afferent volley. Since it is known from the work of Heinbecker, O'Leary and Bishop (1933) and others that the saphenous nerve, apart from a fraction of the *C* fibers contributed by way of the grey rami, is made up exclusively of fibers of dorsal root origin, the possibility appeared to be at hand of obtaining new information about the discharges over the dorsal roots that have previously been described by Gotch and Horsley (1891) and by Matthews (1934).

A few preliminary experiments were performed to establish the validity of the observation and to orient further work. The following results were obtained:

1. Persistence of the discharge in the saphenous nerve, when the stimulating electrodes were transferred in turn to the homolateral tibial or peroneal nerve, showed that the discharge was of a reflex nature.

2. Discharges of the same type in dorsal roots connected only with the cord, when other roots or various peripheral nerves were stimulated, confirmed the involvement of these structures in the reflex.

3. That the potentials led from the saphenous nerve were not produced by movement of the preparation and were not artifacts derived from other nerves or from muscles was shown in a number of ways. (i) The discharge was large. It was clearly visible in a neurogram in which a maximal spike could be recorded. High amplification was not necessary and, therefore, the danger of picking up distant potentials was minimized. (ii) The impulses were readily recorded when a long stretch of nerve was freed from the body and the leads were placed near the cut ends of the nerve with the ground lead in the proximal position, the preparation otherwise being without connection with the ground. (iii) The potentials were still present when the preparation was curarized or when all motor nerves to the hind limbs had been severed. (iv) The reflex discharge was reversibly blocked by cocainization of the nerve central to the leads. (v) When the stimulating electrodes were placed at the end of the nerve and a diphasic lead was made proximal to them, the initial phase of

the discharge was in the direction opposite to that of the initial phase of the afferent volley, showing that the two sets of impulses were being conducted in opposite directions.

After satisfactory proofs had been obtained for the existence of the reflex, a series of experiments was designed with the end in view of learning the properties of the reflex.

METHODS

Nerves in good condition and at body temperature are subject to spontaneous firing if exposed to air and the impulses maintain the spinal cord in a continuously conditioned state, thereby reducing the reflex responses to experimentally induced afferent volleys. In order to obviate this difficulty two methods were employed. When velocities of conduction were of importance and the nerve had to be kept at body temperature, firing was prevented by keeping the nerve in 5 per cent CO_2 in oxygen, as described by Lehmann (1937). When velocities of conduction were not of special significance, it sufficed to allow the exposed portion of the nerve to become equilibrated to the temperatures of the laboratory (25°C.–30°C.), as at these temperatures spontaneous firing is reduced or absent.

Decerebrated cats were used for the greater number of the experiments, but in some cases dial narcosis was employed. With the latter technique the results were not found to exhibit any significant difference from similar experiments performed on decerebrated preparations.

For simultaneous leads the differential input circuit described by Toennies (1938) was employed. As between the several leads on a preparation, the disturbance at any given pair of leads due to potential differences between these leads and a grounded point of the preparation, or between these leads and any other pair of leads, is not more than one-thousandth part of the potential differences in question.

RESULTS

Form of the reflex. The reflex appears at a fixed interval after the stimulus producing the exciting afferent volley, the interval being determined by the sum of the conduction times in the nerve fibers involved in the afferent and efferent arms of the reflex and the central reflex time. In homolateral reflexes excited by strong volleys the action potential of the discharge, whether recorded in the roots or in the saphenous nerve, rises rapidly to a maximum. A peak is reached within 1–2 msec. (Figs. 1, 3, 8, and 11); then the potential declines along a curve which shows two or three secondary crests spaced 2.5–3.5 msec. apart (Fig. 1c, d, g, 3a, 7b, 8b).[1] The total duration of the discharge lasts 20–30 msec.

A typical picture of the reflex produced in the saphenous nerve when the saphenous nerve itself is stimulated is shown in Fig. 1. A portion of the nerve was exposed in the leg and placed on electrodes arranged as in the diagram in Fig. 1a. In this arrangement, the spike set up at the centrally placed stimulating electrodes is conducted to the end of the nerve and there recorded monophasically. It shows the fiber content of the volley which is set up by the same stimulus and conducted toward the central nervous system. About 8 msec. after the stimulus the reflex discharge begins to be recorded. It will be noted that after the first large discharge there is an additional, discrete, wave (Fig. 1c) composed of impulses conducted at a slower velocity. This wave,

[1] While this paper was in press, it was shown by additional experiments that the second and third crests are attributable to the repeated activity of fibers that responded during the first crest.

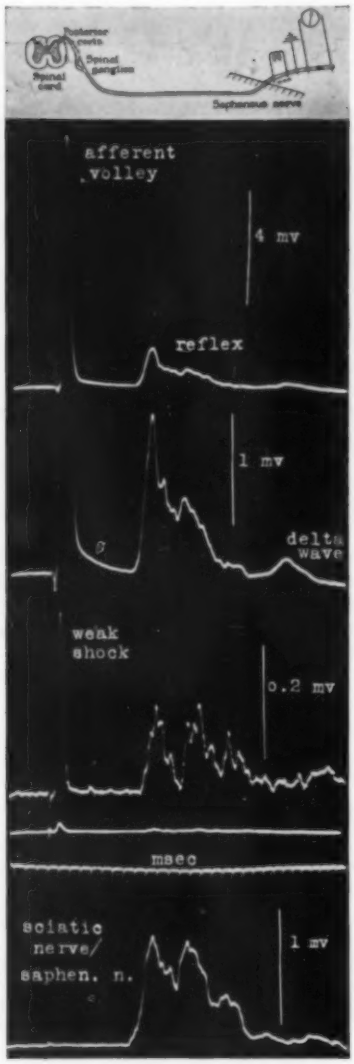

FIG. 1. Dorsal root reflex. Decerebrated cat. *a*, arrangement of electrodes: stimulus and lead on saphenous nerve. *b*, maximal stimulation of alpha fibers with reflex. *c*, same as *b*, but at 4 × the amplification. *d*, weak shock with reflex following: amplification 20 × that of record *b*. *e*, weak shock, recorded with same amplification as *b*. *f*, time 1 msec. each. *g*, stimulus on sciatic nerve, lead on saphenous nerve, amplification as for *c*, speed as for *f*.

which will be shown to be made up of action potentials in delta fibers, is typical of all saphenous to saphenous reflexes; but it is not seen in reflex discharges into the saphenous brought out by afferent volleys in other nerves.

When the reflex is contralateral, a different picture is obtained. The reflex is much smaller, and instead of starting with a burst of impulses, the discharge starts in a few fibers and builds up gradually to a maximum over a period varying between 6 and 20 msec., depending upon the conditions. In Fig. 2 a comparison is made between a homolateral and a contralateral saphenous to saphenous reflex in the same preparation; and in Fig. 3 the reflex discharges in dorsal roots on opposite sides of the lumbar cord, as they are evoked by a shock applied to the sciatic nerve, are brought into contrast.

Reflexes into the dorsal roots can be evoked by stimulation of any one of the adjacent roots of the same or the opposite side. Similarly, reflexes into the saphenous nerve can be elicited by any sensory nerve of the same or opposite limb. The largest reflex, however, is produced when the saphenous nerve itself is stimulated. When shocks of increasing strength are applied, the reflex starts with the first fibers to respond, whether the stimulus is to the saphenous nerve (Fig. 1d) or to some other nerve, and it grows as the number of fibers stimulated increases. During the early period of growth the area of the potential of the reflex discharge is in an approximately linear relationship to the area of the potential of the fibers stimulated. The same rule is followed that was shown by Odoriz to hold for discharges into mixed nerves. Some idea of the magnitude of the reflex can be gained from the observation that when weak stimuli are applied to the saphenous nerve, the area of the potential of reflex origin developing in

the nerve may be considerably larger than the area of the potential resulting from the direct excitation (Fig. 1d). As the strength of stimulus is increased, the rate of increase in the size of the reflex falls off, and the addition of high threshold fibers to those of low threshold produces but little augmentation of the reflex response.

Fibers involved in the reflex. All the velocities of conduction at which impulses are carried in medullated fibers appear to be represented. *C* fibers have not yet been detected. That the fastest fibers in the saphenous nerve are utilized is shown simply by taking leads at two distances from the cord. Fig. 4 shows the difference in the time of arrival of the fastest impulses at points 72 mm. apart when the stimulus was applied to the sciatic nerve. The time difference is 0.85 msec., which means a velocity of 85 m. per sec. (at 37.5°C.).

The involvement of slower velocities is shown by the dispersion of the impulses as conduction proceeds away from the cord. Fig. 5 was obtained from the saphenous nerve. A small opening was made over the nerve 70 mm. from the cord for application of the stimulating electrodes, and 120 mm.

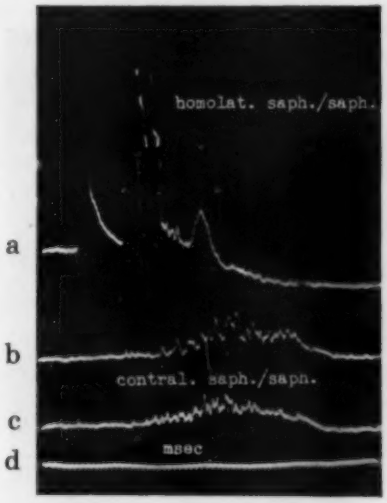

FIG. 2. Comparison between homolateral and contralateral reflex in the saphenous nerve. Decerebrated cat. *a*, stimulus homolateral. *b* and *c*, contralateral stimulus.

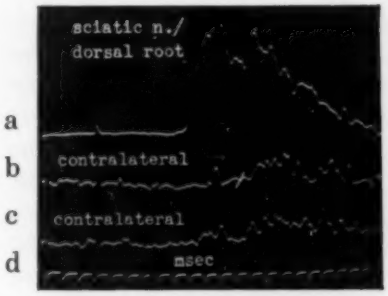

FIG. 3. Comparison between homolateral and contralateral reflex discharges in the dorsal roots of L 6. Decerebrated cat. Stimulus on sciatic nerve: *a*, homolateral root. *b*, simultaneous lead from contralateral root in the same level with 5× amplification. *c*, another record from the contralateral root, showing a somewhat earlier start of the reflex discharge.

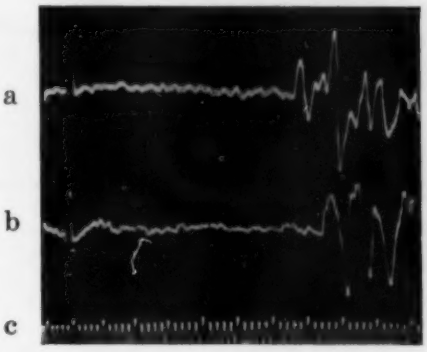

FIG. 4. Conduction speed of the fastest fibers in the reflex discharge of the saphenous nerve, after homolateral sciatic stimulation. Cat under dial. Leads diphasic. *a*, record at proximal lead. *b*, record made simultaneously at a lead 72 mm. distal to *a*. *c*, time in msec. and 0.2 msec.

distal to this point the active lead was applied to a bit of the nerve that had been dissected free. The intervening stretch of nerve was left protected by its coverings. After recording the reflex the conduction distance was shortened, so that the lead came in turn to be 80, 35, and 20 mm. from the position of the stimulus. A notable feature of the records is the second distinct elevation. As conduction proceeds, the second elevation becomes increasingly separated from the first one, showing that it is made up of slower impulses. Calculation of the velocities shows that the head of the group travels at about 19 m. per sec. In other words, the impulses are in the fibers that give the delta elevation in the saphenous electroneurogram, originally designated as the *B* elevation (Erlanger and Gasser, 1929) or the B_1 elevation (Bishop and Heinbecker, 1930). A similar calculation for the velocity of the alpha fibers from the same records gives a value of 78 m. per sec. (35°C.).

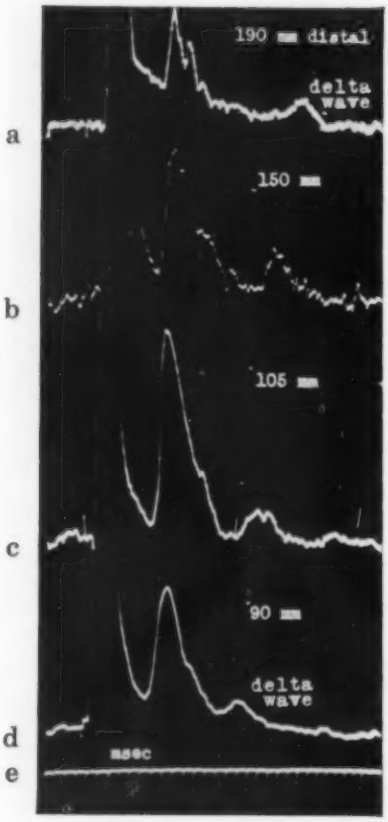

FIG. 5. Conduction speed of the second discharge group (in delta fibers). Stimulus on the saphenous nerve 70 mm. from the spinal cord; leads at the distances from the spinal cord indicated on the records. Cat under dial. The first elevation in all four records is the directly excited afferent volley.

Another method of determining the nature of the fibers occupied during the reflex is to oppose the discharge with a blocking volley of known fiber composition. Fig. 6 shows the effect of opposing a volley of alpha fibers in the saphenous nerve to a reflex discharge into the nerve evoked from the sciatic. During the refractory period of the alpha fibers it is apparent that the discharge attributable to the sciatic stimulation is obliterated. The latter part of this discharge, however, escapes the block and becomes merged with the reflex of saphenous origin which now appears in a modified form, because it is inhibited by the central conditioning effect of the sciatic volley. By placing the blocking alpha volley in various positions with respect to the discharge, it can be shown that all of the first large component of the reflex is carried in alpha fibers.

The second discrete wave described above in the saphenous to saphenous reflex, on the other hand, cannot be blocked by an alpha volley. Active delta fibers are necessary. The simplest form of the experiment involves a single stimulus. When the saphenous nerve is stimulated at a strength that will excite only the fibers which contribute the first high elevation in the electroneurogram, made up of fibers faster than delta (and in this paper called alpha),

a reflex is produced which contains all the components, including the delta group (Fig. 7a). If now the stimulus is increased, so that the exciting volley contains the delta elevation, the delta component of the reflex drops out (Fig. 7b). The afferent delta fibers lag so far behind the alpha fibers that they are

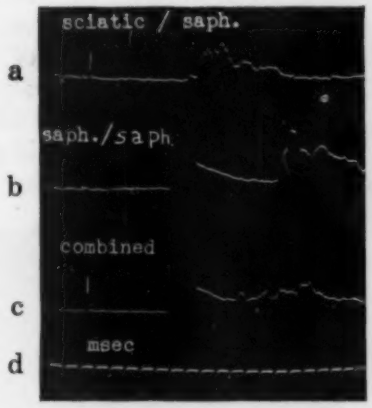

FIG. 6. Blocking effect of alpha fibers. Potentials in the saphenous nerve of a decerebrated cat. *a*, after stimulation of the homolateral sciatic nerve. *b*, after stimulation at alpha strength of the saphenous nerve itself. *c*, both stimuli combined: the saphenous stimulus on the way to the spinal cord meets the reflex impulses coming from the cord.

able to block the reflex discharge into delta fibers which the alpha fibers would produce. In a further refinement of this experiment it can be shown that the delta fibers drop out of the reflex in the proportion in which they are brought into the direct response.

In another form of the experiment, the reflex is produced by an alpha volley as before, and a second volley is employed to produce the blockade. If the blocking volley is made up of only alpha impulses, it is unable to block the second component of the reflex, even when placed directly ahead of the oncoming discharge (Fig. 7c); but if it contains the delta elevation (Fig. 7d) the second component of the reflex is blocked.

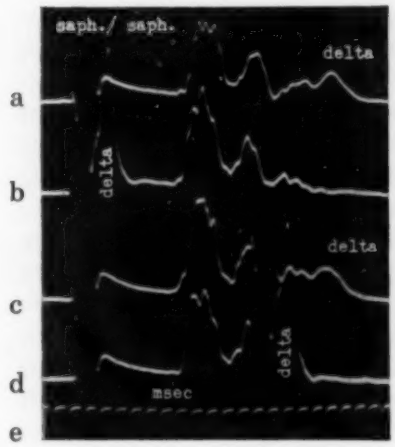

FIG. 7. Blocking effect of delta fibers. All stimuli and leads on the saphenous nerve as in Fig. 1a. Cat under dial. *a*, stimulus at alpha strength; reflex contains delta fiber discharge. *b*, stimulus at strength maximal for delta fibers; the delta fiber discharge is blocked. *c*, as *a*, but with a second afferent alpha volley interpolated during the second wave of the reflex. The delta wave in the reflex is unaffected. *d*, as *a*, but with a second afferent volley including delta fibers interpolated during the second wave of the reflex. The delta fiber discharge is again blocked.

The number of fibers in the dorsal roots participating in the reflex is large. A preliminary estimate of the number involved was made in the following

manner. A saphenous to saphenous reflex was recorded so that the area of the action potentials of the afferent volley and of the reflex discharge could be measured. The size of the afferent volley was adjusted so that all the alpha fibers in the nerve were active, in the manner of the experiment recorded in Fig. 1b. The area of the action potential of the volley thus represented all the alpha fibers in the nerve and served as a suitable reference value with which the first component of the reflex discharge (that has just been shown to be carried exclusively in alpha fibers) could be compared.

The area of the reflex is 65 per cent of the area of the spike (inclusive of the after-potential), but this ratio cannot be taken to represent the proportion of the fibers in the reflex because of the possibility of repetition within individual fibers. The duration of the potential is 8 msec. Therefore, if repetition is taking place, it must occur at frequencies higher than 125 per sec. In the absence of frequencies higher than this figure, 65 per cent would represent the proportion of the fibers involved in the reflex. If higher frequencies occur, they could hardly be expected to be faster than 300 per sec.; that is, one would hardly expect repetition within the compass of the first peak of the reflex potential.[2] The area of the first peak is 35 per cent of the spike area. Thus an estimate that 35 per cent of the alpha fibers are accessible to reflex occupation would be a conservative one, particularly in view of the fact that there is no reason to believe that all the alpha fibers potentially available for reflex activity are involved in this particular reflex.

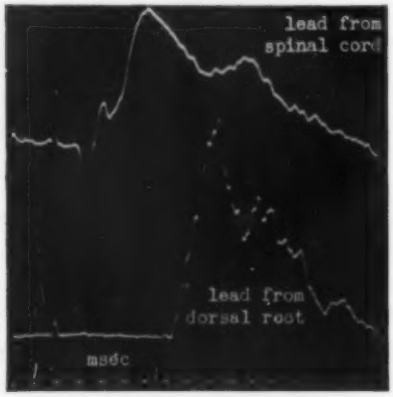

FIG. 8. Reflex time of the dorsal root reflex. Stimulus on sciatic nerve. Cat under dial. *a*, potential on the surface of the spinal cord near entrance of the dorsal roots in L 6 against an average lead outside the spinal cord. The first downward deflection represents the incoming impulses in the sciatic nerve fibers. *b*, simultaneous lead from dorsal root in L 6 about 10 mm. distal from root entrance.

It would be interesting to know whether all the fibers mediate sensory impulses and reflex discharges, or whether some of the fibers are reserved for the latter function only. An answer to this question cannot be given at the present time. All that can be said is that if there are non-sensory fibers in the dorsal roots, they are numerous and distributed over a wide range of velocities.

Reflex time. The reflex time is best studied on roots, as little correction is necessary for conduction in the nerve fibers. A special electrode holder was constructed to clamp on to the vertebra adjacent to the root. It carried a pair of hook-shaped silver electrode wires, which could be adjusted to the proper position for picking up the potentials from the root by means of a three-dimensional slide arrangement operating with keystones and spindles. When

[2] The experiments mentioned in the footnote on page 379 confirm this expectation.

in operation, mechanical disturbance of the roots was minimized, even when large reflex movements took place during the observations.

A homolateral reflex in the sixth lumbar root produced by a shock applied to the sciatic nerve is shown in Fig. 8, along with a simultaneous record of the potential in the spinal cord. The first deflection downward marks the arrival of the afferent impulses at the cord. The large deflection upward is the negative part of the cord potential (Gasser and Graham). The reflex starts 4.2 msec. after the arrival of the impulses. When corrected by 0.2 msec. for the conduction time in the nerve fibers, a figure of 4.0 msec. is obtained for the total synaptic delay in the cord. This, of course, is the minimal reflex time. Other impulses continue to be discharged for the next 20 msec. The minimal reflex time is the same, whether it is produced by a weak or a strong afferent volley and is remarkably constant from preparation to preparation, the variation being less than 1 msec.

The synaptic delay in a contralateral reflex is only slightly longer than in the homolateral reflex. Fig. 3b shows an additional delay of 1.5 msec. in comparison with 3a; and for 3c the additional delay is even less. This interval is long enough, however, on the basis of the unpublished studies of Toennies on the synapse time in the spinal cord, which gave values of 0.55 to 0.8 msec., to allow for the passage of one or two synapses in addition to the number involved in the homolateral reflex. In the latter there is sufficient time for traversing 5 to 6 synapses.

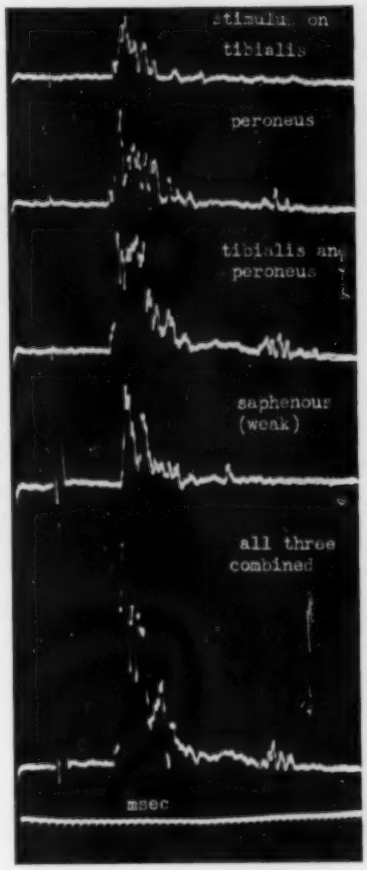

FIG. 9. Summation from simultaneous stimulation of the tibialis, peroneal, and saphenous nerves. All leads from the homolateral saphenous nerve. Decerebrated cat. *a*, stimulation of the tibialis nerve at maximal alpha strength. *b*, stimulation of the peroneal nerve at maximal alpha strength. *c*, simultaneous stimulation of *a* and *b*. *d*, weak stimulation of the saphenous nerve. *e*, simultaneous stimulation of *a*, *b*, and *d*.

Reflex summation. Like motor reflexes, the reflexes over the dorsal roots may be summed and facilitated or inhibited. Fig. 9 shows how, as stimulation of one sensory nerve is added to another, the size of the reflex discharge into the saphenous nerve becomes augmented. Stimulation of the tibial and peroneal nerves produces a greater effect than stimulation of either nerve alone, and the combined effect is further increased if a small afferent volley from the saphenous nerve itself is added to the total. The increase in

the reflex might be brought about through occupation of more pathways in parallel or through summation of excitation at the synapses because of activity in adjacent endings occasioned by convergence of impulses from the several sources. Or it might be brought about by a combination of these two possibilities, or by the two overbalancing a certain amount of inhibition. It is impossible to know from inspection of the records how the effect is constituted. However, it is possible to show that facilitation by appropriately timed convergent impulses can take place; and also that the reflex may be inhibited.

In order to demonstrate facilitation it is necessary to show that the effect of two simultaneous volleys is greater than the sum of the effects of the two volleys in isolation. This condition is met in Fig. 10, in which a dorsal root to dorsal root reflex is facilitated by stimulation of the sciatic nerve. Owing to the longer conduction distance in the sciatic nerve, the first impulses in the volley from this source arrive at the spinal cord 1.2 msec. later than the afferent impulses from the root. As the reflex time is the same in the two instances, the root to root reflex starts earlier than the sciatic to root reflex. When the two sources of the afferent volleys are stimulated simultaneously, it is now seen that in the period during which the root to root reflex antecedes the sciatic nerve to root reflex, the activity in the spinal cord attributable to the impulses from the sciatic nerve is able to increase the reflex discharge of root origin to a size over and above what it would otherwise be.

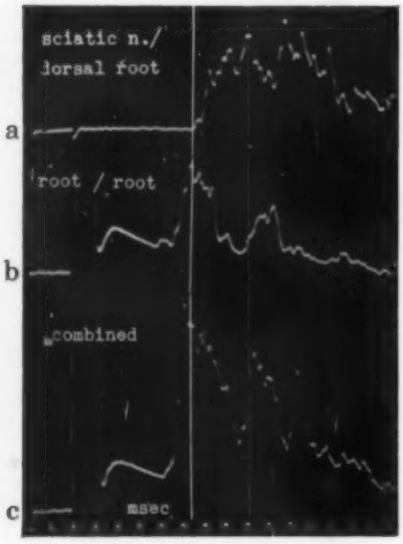

FIG. 10. Facilitation of a reflex discharge into a dorsal root (L 7). Cat under dial. *a*, stimulation of the sciatic nerve. *b*, stimulation of the dorsal root itself. The first impulses arrive at the spinal cord 1.2 msec. earlier than the first impulses from the sciatic nerve. *c*, *a* and *b* combined. The vertical white line marks the time of the first reflex discharge when the sciatic nerve is stimulated. Ahead of this line, the combined reflex is clearly facilitated.

Inhibition. When two afferent volleys are separated by a short time interval, the reflex produced by the second or testing volley is inhibited by the activity ensuing upon the first or conditioning volley. Fig. 11 shows the inhibitory effect of a stimulating shock to the tibial nerve 4 msec. ahead of a shock to the saphenous nerve, when the reflex into the saphenous nerve is under observation. The tibial nerve, itself producing only a small reflex, through its central effects is able to bring about a material reduction in the reflex from the saphenous nerve. The conditioning is most obvious in connection with the delta wave. Although the tibial nerve is unable to excite reflexly any of the delta fibers of the saphenous nerve, it is able to inhibit completely the reflex excitation of these fibers from the saphenous nerve itself. Some of the central pathways

necessary for the reflex must be accessible to tibial excitation and be conditioned thereby in such a way as to make them for the time being unavailable for participation in the reflex.

It was shown by Gasser and Graham that when a single afferent volley arrives at the spinal cord, there is set up in the internuncial neurons a potential which is characterized by an initial negative period, lasting about 20 msec., followed by a positive potential lasting over 100 msec. During the negative period a discharge of impulses occurs into the sciatic nerve (Hughes and Gasser 1934). A cord potential of this sort is shown in Fig. 12, and during the negative period it can be seen that a discharge likewise takes place into a dorsal root.

Hughes and Gasser also showed that as long as the cord potential conditioned by one afferent volley persists, the response to a second volley is inhibited, both in the internuncial neurons and the ventral root reflex, and that the inhibition is greatest at the start and declines over a period of a second. The relationships of the dorsal root reflexes follow in every way those of the ventral root.

When the reflexes are produced in a dorsal root by two alpha volleys from the sciatic nerve, a reflex response to the second volley takes place only when the latter arrives after the completion of the discharge produced by the first volley, *i.e.*, after 10–20 msec. Recovery is slow at first. In Fig. 12 the response in the root 50 msec. after the conditioning volley is only 15 per cent of the unconditioned response. Later the rate of recovery accelerates. At 100 msec. it is 50 per cent, and at 300 msec. 90 per cent. Then the recovery is more gradual and more than a second is needed for its completion. As in the ventral root reflex, the course of the recovery follows temporally that of the internuncial neurons and must be directly dependent upon it. As a whole, the negative cord potential recovers more rapidly than does the reflex, but it must be remembered that the reflex is several neurons removed from the primary neurons, while the potentials in the cord include those in first and second order neurons. The portion of the cord potential that is attributable to higher order neurons does not recover faster than the reflex.

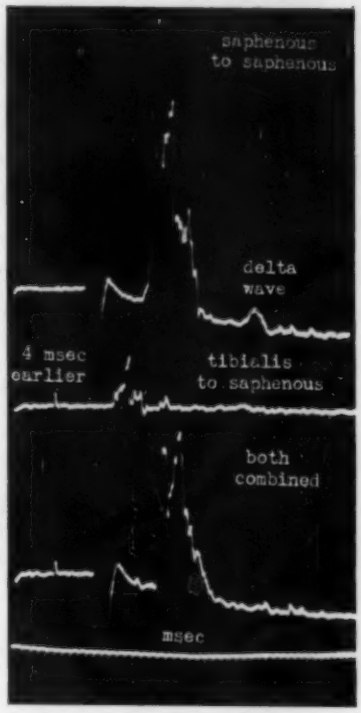

FIG. 11. Inhibition of a saphenous to saphenous reflex by stimulation of the homolateral tibial nerve 4 msec. earlier than the stimulation of the saphenous nerve. *a*, stimulation of the saphenous nerve itself. *b*, stimulation of the tibialis nerve. *c*, *a* and *b* combined. Note the reduction of the alpha group and the elimination of the delta group.

When the reflex in the saphenous nerve is in response to tetanic stimulation of the homolateral sciatic nerve, all the components after the first one are reduced by an amount related to the frequency of the tetanus. Fig. 13 shows the reduction at frequencies of 5 and 12 per sec. As the tetanus proceeds, the discharges tend to decline progressively, that is, conditioning, or inhibition, is cumulative. At low frequencies the decline is small and the successive components tend to arrive at a steady state. But at higher frequencies the decline is rapid and the discharge takes on the form of a typical "jet" reflex.

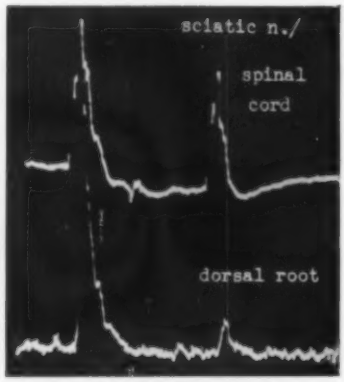

FIG. 12. Simultaneous records of the spinal cord potentials and a dorsal root reflex, showing inhibition of the response to an afferent volley by a response preceding it by 50 msec. Refractoriness of the reflex activity related to the spinal cord potentials. Two shocks of equal strength, maximal for alpha, were applied to the sciatic nerve. Decerebrated cat. *a*, potential at the dorsal surface of the spinal cord at L 6 against surface of cord at L 4. *b*, lead made simultaneously from a strand of the sixth lumbar dorsal root.

DISCUSSION

Reflex discharges over the dorsal roots were originally described by Gotch and Horsley in 1891. With the slow galvanometers then available they demonstrated reflexly excited activity in dorsal roots after the connection with the ganglion had been severed, and in the sciatic nerve after all the ventral roots had been cut. Their conclusion, which we must now admit to be correct, was that "when a spinal center is thrown into activity, a portion of its energy flows as a discharge backwards down the posterior roots as well as forwards down the efferent fibers of the anterior roots and upwards and outwards along internuncial fibers to the next center." But their observation passed unheeded, probably because it stood in opposition to the strongly entrenched law of Bell and Magendie.

Rediscovery of the discharges was made by Matthews in 1934, and a more complete description was given in a paper with Barron in 1935. It was recognized that impulses emerge over the dorsal roots in large numbers; but in the interpretation of the phenomenon an explanation was put forward for the majority of the impulses which did not involve their participation in a reflex. The discharges in the larger fibers were divided into two types: secondary or relayed discharges from cells within the spinal cord (type *c*), and antidromic sensory discharges (type *b*). The type *c*

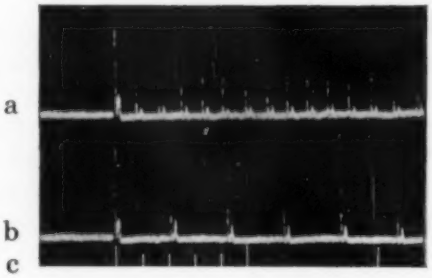

FIG. 13. Response to slow tetanization. Decerebrated cat: Stimulation of the sciatic nerve, lead from the homolateral saphenous nerve. *a*, 12 stimuli per sec. *b*, 4.5 stimuli per sec. *c*, time in 0.1 and 0.5 sec. intervals.

discharges were conceived as having full reflex character. They could be evoked or modified by impulses from widely separated sensory fields on the same or the opposite side of the body, such as the impulses arising from movements of the limbs or head. On the other hand, the major group, or type *b*, was conceived as occurring in fibers that were emerging as a continuation of sensory fibers which had entered the cord through some other root on the same side ("recurrent" fibers). Impulses could be excited in these fibers only from highly restricted areas.

In the course of our observations we have searched for impulses that could be interpreted as being of the recurrent type. The velocities involved are so rapid that impulses entering one root should appear in even quite distant roots within 1 msec. For adjacent roots the time would be a small fraction of a millisecond. But no recurrent impulses have been found. The main discharge, which is a large one, starts regularly after 4+msec. (Figs. 3, 8, and 10a), and even if the amplification is increased up to the noise level, no impulses can be identified as leaving within the first millisecond. Thus the repeated discharges of constant height that are conducted in the centrifugal direction but are not subject to reflex control, which were described by Matthews and which we also have observed in certain preparations, can in our opinion hardly be taking place in recurrent fibers.

The location of the cell bodies from which the fibers involved in the reflex originate cannot be settled by physiological experiment. The evidence must come from histological observation. Hinsey has reviewed the findings and has also performed new experiments of his own. The best supported interpretation appears to be that the fibers arise from cells in the dorsal root ganglia. Since the appearance of Hinsey's review, the subject has been reexamined by Young and Zuckerman. They find a few fibers smaller than 3μ undegenerated after removal of the ganglion, but they consider that the possibility exists that the fibers may have regenerated from the ventral roots. In any case, as they found no large fibers and as the reflex involves the largest fibers in the roots, it must be considered as occurring in fibers having their origins in the dorsal root ganglia. The conclusion seems to be inescapable that fibers from the dorsal root ganglia make central synaptic connections with internuncial neurons of the cord in such a way that they can be reflexly excited with a resulting discharge of impulses toward the periphery of the body. The question whether or not the fibers which carry these impulses are identical with the fibers carrying the sensory impulses toward the cord has not yet been answered by direct experimental evidence.

Summary

1. A description is given of the properties of the reflex discharge which takes place over the spinal dorsal roots of the cat, following stimulation of sensory nerves. Observations were made on the saphenous nerve or on the lumbar roots following stimulation of homolateral or contralateral lumbar roots or sensory nerves of the hind limb.

2. The homolateral reflex produced by a single afferent volley is charac-

terized by an action potential that rises to a peak in 1–2 msec., then declines along a curve which shows two to three secondary crests at intervals of 2.5–3.5 msec. Alpha fibers are involved exclusively in this part of the reflex.

3. When a reflex is produced in the saphenous nerve by a volley of alpha impulses from the saphenous nerve itself, the first reflex wave is followed by a second wave which is separated from it and is carried in delta fibers.

4. The contralateral reflex produced by a single afferent volley is much smaller than the homolateral reflex, but it lasts longer. It starts out gradually and comes to a maximum only after 6–20 msec.

5. The reduced reflex time of the first discharges in the homolateral dorsal root reflex is 4+msec., and is independent of the strength of the exciting volley. In the contralateral reflex the reflex time is as much as 1.5 msec. longer.

6. The reflex produced by an afferent volley can be conditioned by a second appropriately timed afferent volley in the same or another nerve. Summation, facilitation, and inhibition can be demonstrated.

7. A calculation is given indicating that at least 35 per cent of the alpha fibers in the saphenous nerve are accessible to reflex activation.

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